

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :

C12N 15/12, C07K 14/705, C12N 5/10,
A01K 67/027, C12N 15/00, A61K 38/17,
48/00, 38/45, 31/00, 31/70, G01N 33/68,
C12Q 1/68, C12N 15/11

A2

(11) International Publication Number:

WO 00/55318

(43) International Publication Date: 21 September 2000 (21.09.00)

(21) International Application Number: PCT/IB00/00532

(22) International Filing Date: 15 March 2000 (15.03.00)

(30) Priority Data:

60/124,702	15 March 1999 (15.03.99)	US
60/138,048	8 June 1999 (08.06.99)	US
60/139,600	17 June 1999 (17.06.99)	US
60/151,977	1 September 1999 (01.09.99)	US

(71) Applicants: UNIVERSITY OF BRITISH COLUMBIA [CA/CA]; 2329 West Mall, Vancouver, British Columbia V6T 1Z4 (CA). XENON BIORESEARCH, INC. [CA/CA]; NRC Innovation Centre, 3250 East Mall, Vancouver, British Columbia V6T 1W5 (CA).

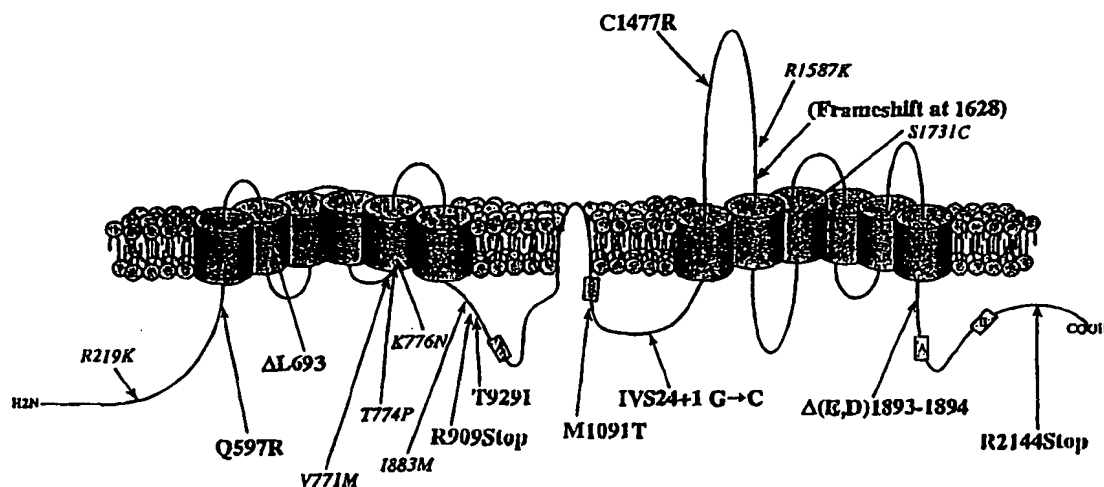
(72) Inventors: HAYDEN, Michael, R.; 4484 West 7th Avenue, Vancouver, British Columbia V6R 1W9 (CA). WILSON, Angela, R.; 7100 Langton Road, Richmond, British Columbia V7C 4B2 (CA). PIMSTONE, Simon, N.; 4746 West 6th Avenue, Vancouver, British Columbia V6T 1C5 (CA).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GII, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: METHODS AND REAGENTS FOR MODULATING CHOLESTEROL LEVELS



Mutation
Polymorphism

(57) Abstract

The invention features ABCI nucleic acids and polypeptides for the diagnosis and treatment of abnormal cholesterol regulation. The invention also features methods for identifying compounds for modulating cholesterol levels in an animal (e.g., a human).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
DY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

METHODS AND REAGENTS FOR MODULATING CHOLESTEROL LEVELS

5

Background of the Invention

Low HDL cholesterol (HDL-C), or hypoalphalipoproteinemia, is a blood lipid abnormality which correlates with a high risk of cardiovascular disease (CVD), in particular coronary artery disease (CAD), but also cerebrovascular disease, coronary restenosis, and peripheral vascular disease. HDL, or 'good cholesterol' levels are influenced by both environmental and genetic factors.

Epidemiological studies have consistently demonstrated that plasma HDL-C concentration is inversely related to the incidence of CAD. HDL-C levels are a strong graded and independent cardiovascular risk factor. Protective effects of an elevated HDL-C persist until 80 years of age. A low HDL-C is associated with an increased CAD risk even with normal (<5.2 mmol/l) total plasma cholesterol levels. Coronary disease risk is increased by 2% in men and 3% in women for every 1 mg/dL (0.026 mmol/l) reduction in HDL-C and in the majority of studies this relationship is statistically significant even after adjustment for other lipid and non-lipid risk factors. Decreased HDL-C levels are the most common lipoprotein abnormality seen in patients with premature CAD. Four percent of patients with premature CAD have an isolated form of decreased HDL-C levels with no other lipoprotein abnormalities while 25% have low HDL levels with accompanying hypertriglyceridemia.

Even in the face of other dyslipidemias or secondary factors, HDL-C levels are important predictors of CAD. In a cohort of diabetics, those with isolated low HDL cholesterol had a 65% increased death rate compared to diabetics with normal HDL cholesterol levels (>0.9 mmol/l). Furthermore, it has been shown that even within high risk populations, such as those with familial hypercholesterolemia, HDL cholesterol level is an important predictor of CAD. Low HDL cholesterol levels thus constitute a major, independent, risk for CAD.

These findings have led to increased attention to HDL cholesterol levels as a focus for treatment, following the recommendations of the National Cholesterol Education Program. These guidelines suggest that HDL cholesterol values below 0.9 mmol/l confer a significant risk for men and women. As such, nearly half of patients with CAD would have low HDL cholesterol. It is therefore crucial that we obtain a better understanding of factors which contribute to this phenotype. In view of the fact that pharmacological intervention of low HDL cholesterol levels has so far proven unsatisfactory, it is also important to understand the factors that regulate these levels in the circulation as this understanding may reveal new therapeutic targets.

Absolute levels of HDL cholesterol may not always predict risk of CAD. In the case of CETP deficiency, individuals display an increased risk of developing CAD, despite increased HDL cholesterol levels. What seems to be important in this case is the functional activity of the reverse cholesterol transport pathway, the process by which intracellular cholesterol is trafficked out of the cell to acceptor proteins such as ApoAI or HDL. Other important genetic determinants of HDL cholesterol levels, and its inverse relation with CAD, may reside in the processes leading to HDL formation and intracellular cholesterol trafficking and efflux. To date, this process is poorly understood, however, and clearly not all of the components of this pathway have been identified. Thus, defects preventing proper HDL-mediated cholesterol efflux may be important predictors of CAD. Therefore it is critical to identify and understand novel genes involved in the intracellular cholesterol trafficking and efflux pathways.

HDL particles are central to the process of reverse cholesterol transport and thus to the maintenance of tissue cholesterol homeostasis. This process has multiple steps which include the binding of HDL to cell surface components, the acquisition of cholesterol by passive absorption, the esterification of this cholesterol by LCAT and the subsequent transfer of esterified cholesterol by CETP, to VLDL and chylomicron remnants for liver uptake. Each of these steps is known to impact the plasma concentration of HDL.

Changes in genes for ApoAI-CIII, lipoprotein lipase, CETP, hepatic lipase, and LCAT all contribute to determination of HDL-C levels in humans. One rare form of genetic HDL deficiency is Tangier disease (TD), diagnosed in approximately 40

patients world-wide, and associated with almost complete absence of HDL cholesterol (HDL-C) levels (listed in OMIM as an autosomal recessive trait (OMIM 205400)).

These patients have very low HDL cholesterol and ApoAI levels, which have been ascribed to hypercatabolism of nascent HDL and ApoAI, due to a delayed acquisition of lipid and resulting failure of conversion to mature HDL. TD patients accumulate cholesterol esters in several tissues, resulting in characteristic features, such as enlarged yellow tonsils, hepatosplenomegaly, peripheral neuropathy, and cholesterol ester deposition in the rectal mucosa. Defective removal of cellular cholesterol and phospholipids by ApoAI as well as a marked deficiency in HDL mediated efflux of intracellular cholesterol has been demonstrated in TD fibroblasts. Even though this is a rare disorder, defining its molecular basis could identify pathways relevant for cholesterol regulation in the general population. The decreased availability of free cholesterol for efflux in the surface membranes of cells in Tangier Disease patients appears to be due to a defect in cellular lipid metabolism or trafficking.

Approximately 45% of Tangier patients have signs of premature CAD, suggesting a strong link between decreased cholesterol efflux, low HDL cholesterol and CAD. As increased cholesterol is observed in the rectal mucosa of persons with TD, the molecular mechanism responsible for TD may also regulate cholesterol adsorption from the gastrointestinal (GI) tract.

A more common form of genetic HDL deficiency occurs in patients who have low plasma HDL cholesterol usually below the 5th percentile for age and sex (OMIM 10768), but an absence of clinical manifestations specific to Tangier disease (Marcil et al., *Arterioscler. Thromb. Vasc. Biol.* 19:159-169, 1999; Marcil et al., *Arterioscler. Thromb. Vasc. Biol.* 15:1015-1024, 1995). These patients have no obvious environmental factors associated with this lipid phenotype, and do not have severe hypertriglyceridemia nor have known causes of severe HDL deficiency (mutations in ApoAI, LCAT, or LPL deficiency) and are not diabetic. The pattern of inheritance of this condition is most consistent with a Mendelian dominant trait (OMIM 10768).

The development of drugs that regulate cholesterol metabolism has so far progressed slowly. Thus, there is a need for a better understanding of the genetic components of the cholesterol efflux pathway. Newly-discovered components can

then serve as targets for drug design.

Low HDL levels are likely to be due to multiple genetic factors. The use of pharmacogenomics in the aid of designing treatment tailored to the patient makes it desirable to identify polymorphisms in components of the cholesterol efflux pathway.

5 An understanding of the effect of these polymorphisms on protein function would allow for the design of a therapy that is optimal for the patient.

Summary of the Invention

10 In a first aspect, the invention features a substantially pure ABC1 polypeptide having ABC1 biological activity. Preferably, the ABC1 polypeptide is human ABC1 (e.g., one that includes amino acids 1 to 60 or amino acids 61 to 2261 of SEQ ID NO: 1). In one preferred embodiment, the ABC1 polypeptide includes amino acids 1 to 2261 of SEQ ID NO: 1.

15 Specifically excluded from the polypeptides of the invention are the polypeptide having the exact amino acid sequence as GenBank accession number CAA10005.1 and the nucleic acid having the exact sequence as AJ012376.1. Also excluded is protein having the exact amino acid sequence as GenBank accession number X75926.

20 In a related aspect, the invention features a substantially pure ABC1 polypeptide that includes amino acids 1 to 2261 of SEQ ID NO: 1.

25 In another aspect, the invention features a substantially pure nucleic acid molecule encoding an ABC1 polypeptide having ABC1 biological activity (e.g., a nucleic acid molecule that includes nucleotides 75 to 254 or nucleotides 255 to 6858 of SEQ ID NO: 2). In one preferred embodiment, the nucleic acid molecule includes nucleotides 75 to 6858 of SEQ ID NO: 2.

In a related aspect, the invention features an expression vector, a cell, or a non-human mammal that includes the nucleic acid molecule of the invention.

30 In yet another aspect, the invention features a substantially pure nucleic acid molecule that includes nucleotides 75 to 254 of SEQ ID NO: 2, nucleotides 255 to 6858 of SEQ ID NO: 2, or nucleotides 75 to 6858 of SEQ ID NO: 2.

In still another aspect, the invention features a substantially pure nucleic acid molecule that includes at least fifteen nucleotides corresponding to the 5' or 3' untranslated region from a human ABC1 gene. Preferably, the 3' untranslated region includes nucleotides 7015-7860 of SEQ ID NO: 2.

5 In a related aspect, the invention features a substantially pure nucleic acid molecule that hybridizes at high stringency to a probe comprising nucleotides 7015-7860 of SEQ ID NO: 2.

10 In another aspect, the invention features a method of treating a human having low HDL cholesterol or a cardiovascular disease, including administering to the human an ABC1 polypeptide, or cholesterol-regulating fragment thereof, or a nucleic acid molecule encoding an ABC1 polypeptide, or cholesterol-regulating fragment thereof. In a preferred embodiment, the human has a low HDL cholesterol level relative to normal. Preferably, the ABC1 polypeptide is wild-type ABC1, or has a mutation increases its stability or its biological activity. A preferred biological
15 activity is regulation of cholesterol.

In a related aspect, the invention features a method of preventing or treating cardiovascular disease, including introducing into a human an expression vector comprising an *ABC1* nucleic acid molecule operably linked to a promoter and encoding an ABC1 polypeptide having ABC1 biological activity.

20 In another related aspect, the invention features a method of preventing or ameliorating the effects of a disease-causing mutation in an *ABC1* gene, including introducing into a human an expression vector comprising an *ABC1* nucleic acid molecule operably linked to a promoter and encoding an ABC1 polypeptide having ABC1 biological activity.

25 In still another aspect, the invention features a method of treating or preventing cardiovascular disease, including administering to an animal (e.g., a human) a compound that mimics the activity of wild-type ABC1 or modulates the biological activity of ABC1.

30 One preferred cardiovascular disease that can be treated using the methods of the invention is coronary artery disease. Others include cerebrovascular disease and peripheral vascular disease.

The discovery that the ABC1 gene and protein are involved in cholesterol transport that affects serum HDL levels allows the ABC1 protein and gene to be used in a variety of diagnostic tests and assays for identification of HDL-increasing or CVD-inhibiting drugs. In one family of such assays, the ability of domains of the ABC1 protein to bind ATP is utilized; compounds that enhance this binding are potential HDL-increasing drugs. Similarly, the anion transport capabilities and membrane pore-forming functions in cell membranes can be used for drug screening.

ABC1 expression can also serve as a diagnostic tool for low HDL or CVD; determination of the genetic subtyping of the *ABC1* gene sequence can be used to subtype low HDL individuals or families to determine whether the low HDL phenotype is related to ABC1 function. This diagnostic process can lead to the tailoring of drug treatments according to patient genotype (referred to as pharmacogenomics), including prediction of the patient's response (e.g., increased or decreased efficacy or undesired side effects upon administration of a compound or drug).

Antibodies to an ABC1 polypeptide can be used both as therapeutics and diagnostics. Antibodies are produced by immunologically challenging a B-cell-containing biological system, e.g., an animal such as a mouse, with an ABC1 polypeptide to stimulate production of anti-ABC1 protein by the B-cells, followed by isolation of the antibody from the biological system. Such antibodies can be used to measure ABC1 polypeptide in a biological sample such as serum, by contacting the sample with the antibody and then measuring immune complexes as a measure of the ABC1 polypeptide in the sample. Antibodies to ABC1 can also be used as therapeutics for the modulation of ABC1 biological activity.

Thus, in another aspect, the invention features a purified antibody that specifically binds to ABC1.

In yet another aspect, the invention features a method for determining whether a candidate compound modulates ABC1 biological activity, comprising: (a) providing an ABC1 polypeptide; (b) contacting the ABC1 polypeptide with the candidate compound; and (c) measuring ABC1 biological activity, wherein altered ABC1 biological activity, relative to an ABC1 polypeptide not contacted with the compound,

indicates that the candidate compound modulates ABC1 biological activity.

Preferably, the ABC1 polypeptide is in a cell or is in a cell-free assay system.

In still another aspect, the invention features a method for determining whether a candidate compound modulates ABC1 expression. The method includes
5 (a) providing a nucleic acid molecule comprising an ABC1 promoter operably linked to a reporter gene; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter gene expression, wherein altered reporter gene expression, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound modulates ABC1 expression.

10 In another aspect, the invention features a method for determining whether candidate compound is useful for modulating cholesterol levels, the method including the steps of: (a) providing an ABC1 polypeptide; (b) contacting the polypeptide with the candidate compound; and (c) measuring binding of the ABC1 polypeptide, wherein binding of the ABC1 polypeptide indicates that the candidate compound is
15 useful for modulating cholesterol levels.

In a related aspect, the invention features method for determining whether a candidate compound mimics ABC1 biological activity. The method includes (a) providing a cell that is not expressing an ABC1 polypeptide; (b) contacting the cell with the candidate compound; and (c) measuring ABC1 biological activity of the cell,
20 wherein altered ABC1 biological activity, relative to a cell not contacted with the compound, indicates that the candidate compound modulates ABC1 biological activity. Preferably, the cell has an *ABC1* null mutation. In one preferred embodiment, the cell is in a mouse or a chicken (e.g., a WHAM chicken) in which its *ABC1* gene has been mutated.

25 In still another aspect, the invention features a method for determining whether a candidate compound is useful for the treatment of low HDL cholesterol. The method includes (a) providing an ABC transporter (e.g., ABC1); (b) contacting the transporter with the candidate compound; and (c) measuring ABC transporter biological activity, wherein increased ABC transporter biological activity, relative to a
30 transporter not contacted with the compound, indicates that the candidate compound is useful for the treatment of low HDL cholesterol. Preferably the ABC transporter is

in a cell or a cell free assay system.

In yet another aspect, the invention features a method for determining whether candidate compound is useful for modulating cholesterol levels. The method includes (a) providing a nucleic acid molecule comprising an ABC transporter promoter operably linked to a reporter gene; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring expression of the reporter gene, wherein increased expression of the reporter gene, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound is useful for modulating cholesterol levels.

In still another aspect, the invention features a method for determining whether a candidate compound increases the stability or decreases the regulated catabolism of an ABC transporter polypeptide. The method includes (a) providing an ABC transporter polypeptide; (b) contacting the transporter with the candidate compound; and (c) measuring the half-life of the ABC transporter polypeptide, wherein an increase in the half-life, relative to a transporter not contacted with the compound, indicates that the candidate compound increases the stability or decreases the regulated catabolism of an ABC transporter polypeptide. Preferably the ABC transporter is in a cell or a cell free assay system.

In a preferred embodiment of the screening methods of the present invention, the cell is in an animal. The preferred ABC transporters are ABC1, ABC2, ABCR, and ABC8, and the preferred biological activity is transport of cholesterol (e.g., HDL cholesterol or LDL cholesterol) or interleukin-1, or is binding or hydrolysis of ATP by the ABC1 polypeptide.

Preferably, the ABC1 polypeptide used in the screening methods includes amino acids 1-60 of SEQ ID NO: 1. Alternatively, the ABC1 polypeptide can include a region encoded by a nucleotide sequence that hybridizes under high stringency conditions to nucleotides 75 to 254 of SEQ ID NO: 2.

In another aspect, the invention features a method for determining whether a patient has an increased risk for cardiovascular disease. The method includes determining whether an *ABC1* gene of the patient has a mutation, wherein a mutation indicates that the patient has an increased risk for cardiovascular disease.

In related aspect, the invention features a method for determining whether a patient has an increased risk for cardiovascular disease. The method includes determining whether an *ABC1* gene of the patient has a polymorphism, wherein a polymorphism indicates that the patient has an increased risk for cardiovascular disease.

In another aspect, the invention features a method for determining whether a patient has an increased risk for cardiovascular disease. The method includes measuring ABC1 biological activity in the patient, wherein increased or decreased levels in the ABC1 biological activity, relative to normal levels, indicates that the patient has an increased risk for cardiovascular disease.

In still another aspect, the invention features a method for determining whether a patient has an increased risk for cardiovascular disease. The method includes measuring ABC1 expression in the patient, wherein decreased levels in the ABC1 expression relative to normal levels, indicates that the patient has an increased risk for cardiovascular disease. Preferably, the ABC1 expression is determined by measuring levels of ABC1 polypeptide or *ABC1* RNA.

In another aspect, the invention features a non-human mammal having a transgene comprising a nucleic acid molecule encoding a mutated ABC1 polypeptide. In one embodiment, the mutation is a dominant-negative mutation.

In a related aspect, the invention features a non-human mammal, having a transgene that includes a nucleic acid molecule encoding an ABC1 polypeptide having ABC1 biological activity.

In another related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding an ABC1 polypeptide having ABC1 biological activity.

In still another aspect, the invention features a method for determining whether a candidate compound decreases the inhibition of a dominant-negative ABC1 polypeptide. The method includes (a) providing a cell expressing a dominant-negative ABC1 polypeptide; (b) contacting the cell with the candidate compound; and (c) measuring ABC1 biological activity of the cell, wherein an increase in the ABC1 biological activity, relative to a cell not contacted with the compound, indicates that

the candidate compound decreases the inhibition of a dominant-negative ABC1 polypeptide.

By "polypeptide" is meant any chain of more than two amino acids, regardless of post-translational modification such as glycosylation or phosphorylation.

5 By "substantially identical" is meant a polypeptide or nucleic acid exhibiting at least 50%, preferably 85%, more preferably 90%, and most preferably 95% identity to a reference amino acid or nucleic acid sequence. For polypeptides, the length of comparison sequences will generally be at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably 10 35 amino acids. For nucleic acids, the length of comparison sequences will generally be at least 50 nucleotides, preferably at least 60 nucleotides, more preferably at least 75 nucleotides, and most preferably 110 nucleotides.

Sequence identity is typically measured using sequence analysis software with the default parameters specified therein (e.g., Sequence Analysis Software Package of 15 the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705). This software program matches similar sequences by assigning degrees of homology to various substitutions, deletions, and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine, valine, isoleucine, leucine; aspartic acid, 20 glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine.

By "high stringency conditions" is meant hybridization in 2X SSC at 40°C with a DNA probe length of at least 40 nucleotides. For other definitions of high stringency conditions, see F. Ausubel et al., *Current Protocols in Molecular Biology*, 25 pp. 6.3.1-6.3.6, John Wiley & Sons, New York, NY, 1994, hereby incorporated by reference.

By "substantially pure polypeptide" is meant a polypeptide that has been separated from the components that naturally accompany it. Typically, the polypeptide is substantially pure when it is at least 60%, by weight, free from the 30 proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the polypeptide is an ABC1 polypeptide that is at least 75%,

more preferably at least 90%, and most preferably at least 99%, by weight, pure. A substantially pure ABC1 polypeptide may be obtained, for example, by extraction from a natural source (e.g., a pancreatic cell), by expression of a recombinant nucleic acid encoding a ABC1 polypeptide, or by chemically synthesizing the protein. Purity
5 can be measured by any appropriate method, e.g., by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

A polypeptide is substantially free of naturally associated components when it is separated from those contaminants that accompany it in its natural state. Thus, a polypeptide which is chemically synthesized or produced in a cellular system different
10 from the cell from which it naturally originates will be substantially free from its naturally associated components. Accordingly, substantially pure polypeptides include those which naturally occur in eukaryotic organisms but are synthesized in *E. coli* or other prokaryotes.

By "substantially pure nucleic acid" is meant nucleic acid that is free of the
15 genes which, in the naturally-occurring genome of the organism from which the nucleic acid of the invention is derived, flank the nucleic acid. The term therefore includes, for example, a recombinant nucleic acid that is incorporated into a vector; into an autonomously replicating plasmid or virus; into the genomic nucleic acid of a prokaryote or a eukaryote cell; or that exists as a separate molecule (e.g., a cDNA or a
20 genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant nucleic acid that is part of a hybrid gene encoding additional polypeptide sequence.

By "modulates" is meant increase or decrease. Preferably, a compound that modulates cholesterol levels (e.g., HDL-cholesterol levels, LDL-cholesterol levels, or
25 total cholesterol levels), or ABC1 biological activity, expression, stability, or degradation does so by at least 10%, more preferably by at least 25%, and most preferably by at least 50%.

By "purified antibody" is meant antibody which is at least 60%, by weight, free from proteins and naturally occurring organic molecules with which it is naturally
30 associated. Preferably, the preparation is at least 75%, more preferably 90%, and most preferably at least 99%, by weight, antibody. A purified antibody may be

obtained, for example, by affinity chromatography using recombinantly-produced protein or conserved motif peptides and standard techniques.

By "specifically binds" is meant an antibody that recognizes and binds to, for example, a human ABC1 polypeptide but does not substantially recognize and bind to other non-ABC1 molecules in a sample, e.g., a biological sample, that naturally includes protein. A preferred antibody binds to the ABC1 polypeptide sequence of Fig. 9A (SEQ ID NO: 1).

By "polymorphism" is meant that a nucleotide or nucleotide region is characterized as occurring in several different forms. A "mutation" is a form of a polymorphism in which the expression level, stability, function, or biological activity of the encoded protein is substantially altered.

By "ABC transporter" or "ABC polypeptide" is meant any transporter that hydrolyzes ATP and transports a substance across a membrane. Preferably, an ABC transporter polypeptide includes an ATP Binding Cassette and a transmembrane region. Examples of ABC transporters include, but are not limited to, ABC1, ABC2, ABCR, and ABC8.

By "ABC1 polypeptide" is meant a polypeptide having substantial identity to an ABC1 polypeptide having the amino acid sequence of SEQ ID NO: 1.

By "ABC biological activity" or "ABC1 biological activity" is meant hydrolysis or binding of ATP, transport of a compound (e.g., cholesterol, interleukin-1) or ion across a membrane, or regulation of cholesterol or phospholipid levels (e.g., either by increasing or decreasing HDL-cholesterol or LDL-cholesterol levels).

The invention provides screening procedures for identifying therapeutic compounds (cholesterol-modulating or anti-CVD pharmaceuticals) which can be used in human patients. Compounds that modulate ABC biological activity (e.g., ABC1 biological activity) are considered useful in the invention, as are compounds that modulate ABC concentration, protein stability, regulated catabolism, or its ability to bind other proteins or factors. In general, the screening methods of the invention involve screening any number of compounds for therapeutically active agents by employing any number of *in vitro* or *in vivo* experimental systems. Exemplary methods useful for the identification of such compounds are detailed below.

The methods of the invention simplify the evaluation, identification and development of active agents for the treatment and prevention of low HDL and CVD. In general, the screening methods provide a facile means for selecting natural product extracts or compounds of interest from a large population which are further evaluated and condensed to a few active and selective materials. Constitutes of this pool are then purified and evaluated in the methods of the invention to determine their HDL-raising or anti-CVD activities or both.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Brief Description of the Drawings

Figs. 1A and 1B are schematic illustrations showing two pedigrees with Tangier Disease, (TD-1 and TD-2). Square and circle symbols represent males and females, respectively. Diagonal lines are placed through the symbols of all deceased individuals. A shaded symbol on both alleles indicates the probands with Tangier Disease. Individuals with half shaded symbols have HDL-C levels at or below the 10th percentile for age and sex, while those with quarter shaded symbols have HDL-C between the 11th and 20th percentiles.

Each individual's ID number, age at the time of lipid measurement, triglyceride level and HDL cholesterol level followed by their percentile ranking for age and sex are listed below the pedigree symbol. Markers spanning the 9q31.1 region are displayed to the left of the pedigree. The affected allele is represented by the darkened bars which illustrate the mapping of the limits of the shared haplotype region as seen in Fig. 3. Parentheses connote inferred marker data, questions marks indicate unknown genotypes, and large arrows show the probands.

Fig. 1C shows ApoAI (10 μ g/mL) -mediated cellular cholesterol efflux in control fibroblasts (n=5, normalized to 100%) and two subjects with Tangier disease (TD). Cells were 3 H-cholesterol (0.2 μ Ci/mL) labeled during growth and cholesterol (20 μ g/mL) loaded in growth arrest. Cholesterol efflux is determined as 3 H medium/(3 H cell + 3 H medium)

Fig. 2A - 2D are schematic illustrations showing four French Canadian pedigrees with FHA (FHA-1 to -4). The notations are as in Fig. 1. Exclamation points on either side of a genotype (as noted in Families FHA-3 and FHA-4) are used when the marker data appears to be inconsistent due to potential microsatellite repeat expansions. A bar that becomes a single thin line suggests that the haplotype is indeterminate at that marker.

Figs. 3A - 3E are a schematic illustration showing a genetic and physical map of 9q31 spanning 35 cM. Fig. 3A: YACs from the region of 9q22-34 were identified and a YAC contig spanning this region was constructed. Fig. 3B: A total of 22 polymorphic CA microsatellite markers were mapped to the contig and used in haplotype analysis in TD-1 and TD-2. Fig 3C: The mutant haplotypes for probands in TD-1 and -2 indicate a significant region of homozygosity in TD-2, while the proband in TD-1 has 2 different mutant haplotypes. The candidate region can be narrowed to the region of homozygosity for CA markers in proband 2. A critical crossover at D9S1690 in TD-1 (A)* also provides a centromeric boundary for the region containing the gene. Three candidate genes in this region (*ABC1*, *LPA-R* and *RGS-3*) are shown. Fig. 3D: Meiotic recombinations in the FHA families (A-H) refine the minimal critical region to 1.2 cM between D9S277 and D9S1866. The heterozygosity of the TD-2 proband at D9S127, which ends a continuous region of homozygosity in TD-2, further refines the region to less than 1 cM. This is the region to which *ABC1* has been mapped. Fig. 3E: Isolated YAC DNA and selected markers from the region were used to probe high-density BAC grid filters, selecting BACs which via STS-content mapping produced an 800 Kb contig. Four BACs containing *ABC1* were sequenced using high-throughput methods.

Fig. 4A shows sequence of one mutation in family TD-1. Patient III-01 is heterozygous for a T to C transition at nucleotide 4503 of the cDNA; the control is homozygous for T at this position. This mutation corresponds to a cysteine to arginine substitution in the *ABC1* protein (C1477R).

Fig 4B shows the amino acid sequence conservation of residue 1477 in mouse and human, but not a related *C. elegans* gene. A change from cysteine to arginine likely has an important effect on the protein secondary and tertiary structure, as noted

by its negative scores in most substitution matrices (Schuler et al., A Practical Guide to the Analysis of Genes and Proteins, eds. Baxeavanis, A.D. & Ouellette, B.F.F. 145:171, 1998). The DNA sequences of the normal and mutant genes are shown above and below the amino acid sequences, respectively.

5 Fig. 4C shows the segregation of the T4503C mutation in TD-1. The presence of the T4503C mutation (+) was assayed by restriction enzyme digestion with *HgaI*, which cuts only the mutant (C) allele (↓). Thus, in the absence of the mutation, only the 194 bp PCR product (amplified between ~ and ~) is observed, while in its presence the PCR product is cleaved into fragments of 134 bp and 60 bp. The
10 proband (individual III.01) was observed to be heterozygous for this mutation (as indicated by both the 194 bp and 134 bp bands), as were his daughter, father, and three paternal cousins. A fourth cousin and three of the father's siblings were not carriers of this mutation.

Fig. 4D shows Northern blot analysis with probes spanning the complete
15 ABC1 gene reveal the expected ~8 Kb transcript and, in addition, a ~3.5 kb truncated transcript only seen in the proband TD-1 and not in TD-2 or control. This was detected by probes spanning exons 1-49 (a), 1-41 (b), 1-22 (c), and 23-29 (d), but not with probes spanning exons 30-41 (e) or 42-49 (f).

Fig. 5A shows the sequence of the mutation in family TD-2. Patient IV-10 is
20 homozygous for an A to G transition at nucleotide 1864 of the cDNA (SEQ ID NO: 2); the control is homozygous for A at this position. This mutation corresponds to a glutamine to arginine substitution in the ABC1 protein (Q597R).

Fig. 5B shows that the glutamine amino acid, which is mutated in the TD-2
25 proband, is conserved in human and mouse ABC1 as well as in an ABC orthologue from *C. elegans*, revealing the specific importance of this residue in the structure/function of this ABC protein in both worms and mammals. The DNA sequences of the normal and mutant proteins are shown above and below the amino acid sequences, respectively.

Fig. 5C shows the segregation of the A1864G mutation in TD-2. The
30 presence of the A1864G mutation (indicated by +) was assayed by restriction enzyme digestion with *AciI*. The 360 bp PCR product has one invariant *AciI* recognition site

(1), and a second one is created by the A1864G mutation. The wild-type allele is thus cleaved to fragments of 215 bp and 145 bp, while the mutant allele (G-allele) is cleaved to fragments of 185 bp, 145 bp and 30 bp. The proband (individual IV-10), the product of a consanguineous mating, was homozygous for the A1864G mutation (+/+), as evidenced by the presence of only the 185 bp and 145 bp bands, while four other family members for whom DNA was tested are heterozygous carriers of this mutation (both the 215 bp and 185 bp fragments were present). Two unaffected individuals (-/-), with only the 215 bp and 145 bp bands are shown for comparison.

Fig. 6A shows a sequence of the mutation in family FHA-1. Patient III-01 is heterozygous for a deletion of nucleotides 2151-2153 of the cDNA (SEQ ID NO: 2). This deletion was detected as a superimposed sequence starting at the first nucleotide after the deletion. This corresponds to deletion of leucine 693 in the ABC1 protein (SEQ ID NO: 1).

Fig. 6B is an alignment of the human and mouse wild-type amino acid sequences, showing that the human and mouse sequences are identical in the vicinity of Δ L693. L693 is also conserved in *C. elegans*. This highly conserved residue lies within a predicted transmembrane domain. The DNA sequences of the normal and mutant proteins are shown above and below the amino acid sequences, respectively.

Fig. 6C shows segregation of the Δ L693 mutation in FHA-1, as assayed by *Eco*RI restriction digestion. Two invariant *Eco*RI restriction sites (indicated by 1) are present within the 297 bp PCR product located between the horizontal arrows (--) while a third site is present in the wild-type allele only. The presence of the mutant allele is thus distinguished by the presence of a 210 bp fragment (+), while the normal allele produces a 151 bp fragment (-). The proband of this family (III.01) is heterozygous for this mutation, as indicated by the presence of both the 210 and 151 bp bands.

Fig. 6D shows a sequence of the mutation in family FHA-3. Patient III-01 is heterozygous for a deletion of nucleotides 5752-5757 of the cDNA (SEQ ID NO: 2). This deletion was detected as a superimposed sequence starting at the first nucleotide after the deletion. This corresponds to deletion of glutamic acid 1893 and aspartic acid 1894 in the ABC1 protein (SEQ ID NO: 1).

Fig. 6E is an alignment of the human and mouse wild-type amino acid sequences, showing that the human and mouse sequences are identical in the vicinity of $\Delta 5752-5757$. This region is highly conserved in *C. elegans*. The DNA sequences of the normal and mutant proteins are shown above and below the amino acid sequences, respectively.

Fig. 6F shows a sequence of the mutation in family FHA-2. Patient III-01 is heterozygous for a C to T transition at nucleotide 6504 of the cDNA (SEQ ID NO: 2). This alteration converts an arginine at position 2144 of SEQ ID NO: 1 to a STOP codon, causing truncation of the last 118 amino acids of the ABC1 protein.

Figs. 7A and 7B show cholesterol efflux from human skin fibroblasts treated with ABC1 antisense oligonucleotides. Fibroblasts from a control subject were labeled with ^3H cholesterol (0.2 $\mu\text{Ci/mL}$) during growth for 48 hours and transfected with 500 nM ABC1 antisense AN-1 (5'-GCA GAG GGC ATG GCT TTA TTT G-3'; SEQ ID NO: 3) with 7.5 μg lipofectin for 4 hours. Following transfection, cells were cholesterol loaded (20 $\mu\text{g/mL}$) for 12 hours and allowed to equilibrate for 6 hours. Cells were either then harvested for total RNA and 10 μg was used for Northern blot analysis. Cholesterol efflux experiments were carried out as described herein. Fig. 7A: AN-1 was the oligonucleotide that resulted in a predictable decrease in ABC1 RNA transcript levels. Fig. 7B: A double antisense transfection method was used. In this method, cells were labeled and transfected with AN-1 as above, allowed to recover for 20 hours, cholesterol loaded for 24 hours, and then re-transfected with AN-1. Twenty hours after the second transfection, the cholesterol efflux as measured. A ~50% decrease in ABC1 transcript levels was associated with a significant decrease in cholesterol efflux intermediate between that seen in wild-type and TD fibroblasts.

Fig. 7C shows show cholesterol efflux from human skin fibroblasts treated with antisense oligonucleotides directed to the region encoding the amino-terminal 60 amino acids. Note that the antisense oligonucleotide AN-6, which is directed to the previously unrecognized translation start site, produces a substantial decrease in cellular cholesterol efflux.

Fig. 8 is a schematic illustration showing predicted topology, mutations, and polymorphisms of ABC1 in Tangier disease and FHA. The two transmembrane and

ATP binding domains are indicated. The locations of mutations are indicated by the arrows with the amino acid changes, which are predicted from the human *ABC1* cDNA sequence. These mutations occur in different regions of the ABC1 protein.

5 Fig. 9A shows the amino acid sequence of the human ABC1 protein (SEQ ID NO: 1).

Figs. 9B - 9E show the nucleotide sequence of the human *ABC1* cDNA (SEQ ID NO: 2).

Fig. 10 shows the 5' and 3' nucleotide sequences suitable for use as 5' and 3' PCR primers, respectively, for the amplification of the indicated ABC1 exon.

10 Fig. 11 shows a summary of alterations found in ABC1, including sequencing errors, mutations, and polymorphisms.

Fig. 12 shows a series of genomic contigs (SEQ ID NOS. 14-29) containing the ABC1 promoter (SEQ ID NO: 14), as well as exons 1-49 (and flanking intronic sequence) of ABC1. The exons (capitalized letters) are found in the contigs as follows: SEQ ID NO: 14--exon 1; SEQ ID NO: 15--exon 2; SEQ ID NO: 16--exon 3; SEQ ID NO: 17--exon 4; SEQ ID NO: 18--exon 5; SEQ ID NO: 19--exon 6; SEQ ID NO: 20--exons 7 and 8; SEQ ID NO: 21--exons 9 through 22; SEQ ID NO: 22--exons 23 through 28; SEQ ID NO: 23--exon 29; SEQ ID NO: 24--exons 30 and 31; SEQ ID NO: 25--exon 32; SEQ ID NO: 26--exons 33 through 36; SEQ ID NO: 27--exons 37 through 41; SEQ ID NO: 28--exons 42-45; SEQ ID NO: 29--exons 46-49.

20 Fig. 13 is a series of illustrations showing that the amino-terminal 60 amino acid region of ABC1 is protein-coding. Lysates of normal human fibroblasts were immunoblotted in parallel with a rabbit polyclonal antibody to amino acids 1-20 of human ABC1 (1); a rabbit polyclonal antibody to amino acids 1430-1449 of human ABC1 (2); and a mouse monoclonal antibody to amino acids 2236-2259 of human ABC1. The additional bands detected in lane 2 may be due to a lack of specificity of that antibody or the presence of degradation products of ABC1.

25 Fig. 14 is a schematic illustration showing that the WHAM chicken contains a non-conservative substitution (G265A) resulting in an amino acid change (E89K).

30 Fig. 15 is a schematic illustration showing that the mutation in the WHAM chicken is at an amino acid that is conserved among human, mouse, and chicken.

Fig. 16 show a summary of locations of consensus transcription factor binding sites in the human ABC1 promoter (nucleotides 1-8238 of SEQ ID NO: 14). The abbreviations are as follows: PPRE=peroxisome proliferator-activated receptor. SRE=steroid response element-binding protein site. ROR=RAR-related orphan receptor.

Detailed Description

Genes play a significant role influencing HDL levels. Tangier disease (TD) was the first reported genetic HDL deficiency. The molecular basis for TD is unknown, but has been mapped to 9q31 in three families. We have identified two additional probands and their families, and confirmed linkage and refined the locus to a limited genomic region. Mutations in the *ABC1* gene accounting for all four alleles in these two families were detected. A more frequent cause of low HDL levels is a distinct disorder, familial HDL deficiency (FHA). On the basis of independent linkage, meiotic recombinants and disease associated haplotypes, FHA was localized to a small genomic region encompassing the *ABC1* gene. A mutation in a conserved residue in ABC1 segregated with FHA. Antisense reduction of the *ABC1* transcript in fibroblasts was associated with a significant decrease in cholesterol efflux.

Cholesterol is normally assembled with intracellular lipids and secreted, but in TD the process is diverted and cholesterol is degraded in lysosomes. This disturbance in intracellular trafficking of cholesterol results in an increase in intracellular cholesterol ester accumulation associated with morphological changes of lysosomes and the Golgi apparatus and cholesteryl ester storage in histiocytes, Schwann cells, smooth muscle cells, mast cells and fibroblasts.

The clinical and biochemical heterogeneity in patients with TD has led to the possibility that genetic heterogeneity may also underlie this disorder. Considering this, we initially performed linkage analysis on these two families of different ancestries (TD-1 is Dutch, TD-2 is British; Frohlich et al., Clin. Invest. Med. 10:377-382, 1987) and confirmed that the genetic mutations underlying TD in these families were localized to the same 9q31 region, to which a large family with TD had been

assigned (Rust et al., Nature Genetics 20:96-98, 1998). Detailed haplotype analysis, together with the construction of a physical map, refined the localization of this gene. Mutations in the ABC1 gene were found in TD.

5 FHA is much more common than TD, although its precise frequency is not known. While TD has been described to date in only 40 families, we have identified more than 40 FHA families in the Netherlands and Quebec alone. After initial suggestions of linkage to 9q31, thirteen polymorphic markers spanning approximately 10 cM in this region were typed and demonstrated the highest LOD score at D9S277. Analysis of the homozygosity of markers in the TD-2 proband, who was expected to
10 be homozygous for markers close to TD due to his parents' consanguinity, placed the TD gene distal to D9S127. Combined genetic data from TD and FHA families pointed to the same genomic segment spanning approximately 1,000 kb between D9S127 and D9S1866. The *ABC1* transporter gene was contained within the minimal genomic region. RT-PCR analysis in one family demonstrated a deletion of leucine at
15 residue 693 ($\Delta 693$) in the first transmembrane domain of ABC1, which segregated with the phenotype of HDL deficiency in this family.

 ABC1 is part of the ATP-binding cassette (ABC transporter) superfamily, which is involved in energy-dependent transport of a wide variety of substrates across membranes (Dean et al., Curr. Opin. Gen. Dev. 5:779-785, 1995). These proteins
20 have characteristic motifs conserved throughout evolution which distinguish this class of proteins from other ATP binding proteins. In humans these genes essentially encode two ATP binding segments and two transmembrane domains (Dean et al., Curr. Opin. Gen. Dev. 5:779-785, 1995). We have now shown that the ABC1 transporter is crucial for intracellular cholesterol transport.

25 We have demonstrated that reduction of the *ABC1* transcript using oligonucleotide antisense approaches results in decreased efflux, clearly demonstrating the link between alterations in this gene and its functional effects. TD and FHA now join the growing list of genetic diseases due to defects in the ABC group of proteins including cystic fibrosis (Zielenski, et al., Annu. Rev. Genet.
30 29:777-807, 1995), adrenoleukodystrophy (Mosser et al., Nature 361: 726-730, 1993), Zellweger syndrome (Gärtner et al., Nat. Genet. 1:23, 1992), progressive familial

intrahepatic cholestasis (Bull et al., Nat. Genet. 18:219-224, 1998), and different eye disorders including Stargardt disease (Allikmets et al., Nat. Genet. 15:236-246, 1997), autosomal recessive retinitis pigmentosa (Allikmets et al., Science 277:1805-1807, 1997), and cone-rod dystrophy (Cremers et al., Hum. Mol. Genet. 7:355-362, 1998).

5 Patients with TD have been distinguished from patients with FHA on the basis that Tangier disease was an autosomal recessive disorder (OMIM 20540) while FHA is inherited as an autosomal dominant trait (OMIM 10768). Furthermore, patients with TD have obvious evidence for intracellular cholesterol accumulation which is not seen in FHA patients. It is now evident that heterozygotes for TD do have reduced HDL levels and that the same mechanisms underlie the HDL deficiency and cholesterol efflux defects seen in heterozygotes for TD as well as FHA. Furthermore, the more severe phenotype in TD represents loss of function from both alleles of the *ABCI* gene.

15 ABC1 is activated by protein kinases, presumably via phosphorylation, which also provides one explanation for the essential role of activation of protein kinase C in promoting cholesterol efflux (Drobnick et al., Arterioscler. Thromb. Vasc. Biol. 15: 1369-1377, 1995). Brefeldin, which inhibits trafficking between the endoplasmic reticulum and the Golgi, significantly inhibits cholesterol efflux, essentially reproducing the effect of mutations in ABC1, presumably through the inhibition of ABC1 biological activity. This finding has significance for the understanding of mechanisms leading to premature atherosclerosis. TD homozygotes develop premature coronary artery disease, as seen in the proband of TD-1 (III-01) who had evidence for coronary artery disease at 38 years. This is particularly noteworthy as TD patients, in addition to exhibiting significantly reduced HDL, also have low LDL cholesterol, and yet they develop atherosclerosis despite this. This highlights the importance of HDL intracellular transport as an important mechanism in atherogenesis. There is significant evidence that heterozygotes for TD are also at increased risk for premature vascular disease (Schaefer et al., Ann. Int. Med. 93:261-266, 1980; Serfaty-Lacroisniere et al., Atherosclerosis 107:85-98, 1994). There is also preliminary evidence for premature atherosclerosis in some probands with FHA (Fig. 2B), e.g., the proband in FHA-2 (III-01) had a coronary artery bypass graft at 46 years

while the proband in FHA-3 (Fig. 2C) had evidence for CAD around 50 years of age. The TD-1 proband had more severe efflux deficiency than the TD-2 proband (Fig. 1C). Interestingly, the TD-2 proband had no evidence for CAD by 62 when he died of unrelated causes, providing preliminary evidence for a relationship between the degree of cholesterol efflux (mediated in part by the nature of the mutation) and the likelihood of atherosclerosis.

The *ABC1* gene plays a crucial role in cholesterol transport and, in particular, intracellular cholesterol trafficking in monocytes and fibroblasts. It also appears to play a significant role in other tissues such as the nervous system, GI tract, and the cornea. Completely defective intracellular cholesterol transport results in peripheral neuropathy, corneal opacities, and deposition of cholesterol esters in the rectal mucosa.

HDL deficiency is heterogeneous in nature. The delineation of the genetic basis of TD and FHA underlies the importance of this particular pathway in intracellular cholesterol transport, and its role in the pathogenesis of atherosclerosis. Unraveling of the molecular basis for TD and FHA defines a key step in a poorly defined pathway of cholesterol efflux from cells and could lead to new approaches to treatment of patients with HDL deficiency in the general population.

HDL has been implicated in numerous other biological processes, including but not limited to: prevention of lipoprotein oxidation; absorption of endotoxins; protection against *Trypanosoma brucei* infection; modulation of endothelial cells; and prevention of platelet aggregation (see Genest et al., J. Invest. Med. 47: 31-42, 1999, hereby incorporated by reference). Any compound that modulates HDL levels may be useful in modulating one or more of the foregoing processes. The present discovery that ABC1 functions to regulate HDL levels links, for the first time, ABC1 with the foregoing processes.

The following examples are to illustrate the invention. They are not meant to limit the invention in any way.

Analysis of TD Families

Studies of cholesterol efflux

Both probands had evidence of marked deficiency of cholesterol efflux similar to that previously demonstrated in TD patients (Fig. 1C). TD-1 is of Dutch descent while TD-2 is of British descent.

Linkage analysis and establishment of a physical map

Multiple DNA markers were genotyped in the region of 9q31 to which linkage to TD had been described (Rust et al., Nat. Genet. 20, 96-98, 1998). Two point linkage analysis gave a maximal peak LOD score of 6.49 at D9S1832 (Table 1) with significant evidence of linkage to all markers in a ~10 cM interval. Recombination with the most proximal marker, D9S1690 was seen in II-09 in Family TD-1 (A* in Fig. 3D) providing a centromeric boundary for the disease gene. Multipoint linkage analysis of these data did not increase the precision of the positioning of the disease trait locus.

A physical map spanning approximately 10 cM in this region was established with the development of a YAC contig (Fig. 3A). In addition, 22 other polymorphic multi-allelic markers which spanned this particular region were mapped to the contig (Fig. 3B) and a subset of these were used in construction of a haplotype for further analysis (Figs. 1A and 1B; Table 2).

While the family of Dutch decent did not demonstrate any consanguinity, the proband in TD-2 was the offspring of a first-cousin consanguineous marriage (Fig. 1B). We postulated, therefore, that it was most likely that this proband would be homozygous for the mutation while the proband in the Dutch family was likely to be a compound heterozygote. The Dutch proband shows completely different mutation bearing haplotypes, supporting this hypothesis (Fig. 3C).

The TD-2 proband was homozygous for all markers tested (Fig. 1B) distal to D9S127 but was heterozygous at D9S127 and DNA markers centromeric to it (Fig. 3C). This suggested that the gene for TD was likely located to the genomic region telomeric of D9S127 and encompassed by the markers demonstrating homozygosity (Fig. 3B).

TABLE 1

Two Point Linkage Analysis of TD-1 and TD-2

Marker Locus	LOD Score at recombination fraction						
	0	0.01	0.05	0.10	0.20	0.30	0.40
<i>D9S1690</i>	-infini	4.25	4.52	4.26	3.39	2.30	1.07
<i>D9S277</i>	6.22	6.11	5.67	5.10	3.90	2.60	1.17
<i>D9S1866</i>	4.97	4.87	4.49	4.00	2.96	1.85	0.70
<i>D9S1784</i>	5.50	5.40	5.00	4.47	3.36	2.17	0.92
<i>D9S1832</i>	6.49	6.37	5.91	5.31	4.05	2.69	1.21
<i>D9S1677</i>	4.60	4.51	4.18	3.76	2.88	1.93	0.93

Results of pairwise linkage analysis using MLINK. Values correspond to the LOD score for linkage between the disease locus and a marker locus for specified values of the recombination fraction.

TABLE 2. Microsatellite markers used in this study

Genetic Markers	Type	Heterozygosity	Number of alleles	Allele frequency* size, bp (proportion)
D9S283	CA	0.80	10	179(0.04); 181(0.34); 183(0.19); 185(0.20); 189(0.05); 193(0.04); 197(0.07); 199(0.02); 201(0.04); 203(0.04)
D9S176	CA	0.82	9	129(0.03); 131(0.16); 133(0.24); 135(0.12); 137(0.25); 139(0.03); 141(0.01); 145(0.05); 147(0.05)
D9S1690	CA	0.79	8	225(0.38); 227(0.14); 229(0.07); 231(0.12); 233(0.05); 235(0.16); 237(0.05); 239(0.05)
D9S277	CA	0.89	15	167(0.07); 171(0.02); 173(0.15); 175(0.11); 177(0.07); 179(0.04); 181(0.17); 183(0.06); 185(0.02); 187(0.02); 189(0.13); 191(0.13); 193(0.02); 197(0.00); 199(0.00)
D9S127	CA	0.72	6	149(0.11); 151(0.07); 153(0.23); 155(0.05); 157(0.45); 159(0.06)
D9S306	CA	0.87	13	102(0.06); 104(0.01); 110(0.03); 112(0.05); 114(0.16); 116(0.15); 118(0.11); 120(0.23); 122(0.06); 124(0.06); 126(0.03); 134(0.02); 136(0.01)
D9S1866	CA	0.62	11	248(0.06); 252(0.04); 254(0.01); 256(0.58); 258(0.03); 260(0.06); 262(0.02); 264(0.12); 266(0.06); 268(0.03); 270(0.01)
D9S1784	CA	0.86	15	174(0.10); 176(0.02); 178(0.00); 180(0.05); 182(0.11); 184(0.23); 186(0.15); 188(0.06); 190(0.04); 192(0.07); 194(0.04); 196(0.07); 198(0.01); 200(0.01); 202(0.01)
AFMa107x19	CA	n.a.	n.a.	n.a.
D9S2170	CA	n.a.	n.a.	n.a.
D9S2171	CA	n.a.	n.a.	n.a.
D9S2107	CA	0.63	5	n.a.
D9S172	CA	0.54	5	291(0.00); 297(0.05); 299(0.22); 303(0.62); 305(0.02)
D9S2109	CA	0.51	3	1(0.42); 2(0.56); 3(0.02)
D9S1832	CA	0.88	12	161(0.04); 163(0.02); 167(0.02); 169(0.04); 171(0.10); 173(0.09); 175(0.15); 177(0.28); 179(0.19); 181(0.04); 183(0.01); 185(0.01)
D9S1835	CA	0.48	4	110(0.02); 112(0.23); 116(0.58); 118(0.07)
D9S1801	CA	0.77	10	166(0.10); 172(0.04); 174(0.02); 182(0.02); 184(0.19); 186(0.40); 188(0.15); 190(0.04); 192(0.02); 194(0.02)
D9S261	CA	0.65	7	90(0.02); 92(0.32); 94(0.02); 98(0.02); 100(0.29); 102(0.04); 104(0.08)
D9S160	CA	0.62	6	136(0.25); 138(0.53); 140(0.01); 142(0.12); 144(0.00); 146(0.07)
D9S1677	CA	0.81	10	251(0.27); 257(0.27); 259(0.07); 261(0.09); 263(0.27); 265(0.14); 267(0.02); 269(0.02); 271(0.04); 273(0.02)
D9S279	CA	0.78	6	244(0.09); 246(0.18); 248(0.29); 250(0.29); 252(0.07); 254(0.09)
D9S275	CA	0.62	4	190(0.31); 196(0.07); 198(0.12); 200(0.09)

* In a Caucasian population of French Canadian or French descent (J. Weissenbach, Personal Communication 1993).
n.a = not assessed.

These polymorphic microsatellite markers were used for DNA typing in the region of 9q31 seen in Fig.3. The majority come from the last version of the Génethon human linkage map³³. The frequency of heterozygosity, the number of alleles as well as the allele frequency of each marker are presented.

Mutation detection

Based on the defect in intracellular cholesterol transport in patients with TD, we reviewed the EST database for genes in this region which might be relevant to playing a role in this process. One gene that we reviewed as a candidate was the lysophosphatidic acid (LPA) receptor (*EDG2*) which mapped near D9S1801 (Fig. 3C). This receptor binds LPA and stimulates phospholipase-C (PLC), and is expressed in fibroblasts. It has previously been shown that the coordinate regulation of PLC that is necessary for normal HDL3 mediated cholesterol efflux is impaired in TD (Walter et al., J. Clin. Invest. 98:2315-2323, 1996). Therefore this gene represented an excellent candidate for the TD gene. Detailed assessment of this gene, using Northern blot and RT-PCR and sequencing analysis, revealed no changes segregating with the mutant phenotype in this family, in all likelihood excluding this gene as the cause for TD. Polymorphisms were detected, however, in the RT-PCR product, indicating expression of transcripts from both alleles.

The second candidate gene (*RGS3*) encodes a member of a family regulating G protein signaling which could also be involved in influencing cholesterol efflux (Mendez et al., Trans. Assoc. Amer. Phys. 104:48-53, 1991). This gene mapped 0.7 cM telomeric to the LPA-receptor (Fig. 3C), and is expressed in fibroblasts. It was assessed by exon-specific amplification, as its genomic organization was published (Chatterjee et al., Genomics 45:429-433, 1997). No significant sequence changes were detected.

The *ABCI* transporter gene had previously been mapped to 9q31, but its precise physical location had not been determined (Luciani et al., Genomics 21:150-159, 1994). The *ABCI* gene is a member of the ATP binding cassette transporters which represents a super family of highly conserved proteins involved in membrane transport of diverse substrates including amino acids, peptides, vitamins and steroid hormones (Luciani et al., Genomics 21:150-159, 1994; Dean et al., Curr. Opin. Gen. Dev. 5:779-785, 1995). Primers to the 3' UTR of this gene mapped to YACs spanning D9S306 (887-B2 and 930-D3) compatible with it being a strong candidate for TD. We initiated large scale genomic sequencing of BACs spanning approximately 800 kb around marker D9S306 (BACs 269, 274, 279 and 291) (Fig

3E). The *ABC1* gene was revealed encompassing 49 exons and a minimum of 75 Kb of genomic sequence. In view of the potential function of a gene in this family as a cholesterol transporter, its expression in fibroblasts and localization to the minimal genomic segment underlying TD, we formally assessed ABC1 as a candidate.

5 Patient and control total fibroblast RNA was used in Northern blot analysis and RT-PCR and sequence analyses. RT-PCR and sequence analysis of TD-1 revealed a heterozygous T to C substitution (Fig. 4A) in the TD-1 proband, which would result in a substitution of arginine for cysteine at a conserved residue between mouse and man (Fig. 4B). This mutation, confirmed by sequencing exon 30 of the
10 *ABC1* gene, exhibited complete segregation with the phenotype on one side of this family (Fig. 4C). This substitution creates a *HgaI* site, allowing for RFLP analysis of amplified genomic DNA and confirmation of the mutation (Fig. 4C). The point mutation in exon 30 was not seen on over 200 normal chromosomes from unaffected persons of Dutch decent, and 250 chromosomes of Western European decent,
15 indicating it is unlikely to be a polymorphism. Northern blot analysis of fibroblast RNA from this patient, using a cDNA encompassing exons 1 to 49 of the gene, revealed a normal sized ~8 Kb transcript and a truncated mutant transcript which was not visible in control RNA or in RNA from other patients with HDL deficiency (Fig. 4D). Additionally, Northern blot analysis using clones encompassing discrete regions
20 of the cDNA revealed that the mutant transcript was detected with a cDNA compassing exons 1 to 49 (a), 1 to 41 (b), 1 to 22 (c), much more faintly with a probe spanning exon 23 to 29 (d) and not seen with probes encompassing exons 30 to 42 (e), but not seen with cDNA fragment spanning exons 30 to 49 (f). This was repeated on multiple filters with control RNA, RNA from other patients with HDL deficiency and
25 the other TD proband, and only in TD-1 was the truncated transcript observed. Sequence analysis of the coding region did not reveal an alteration in sequence that could account for this finding. Furthermore, DNA analysis by Southern blot did not reveal any major rearrangements. Completion of exon sequencing in genomic DNA showed that this mutation was a G to C transversion at position (+1) of intron 24,
30 (Fig. 11) affecting a splice donor site and causing aberrant splicing.

RT-PCR analysis of fibroblast RNA encoding the *ABC1* gene from the

proband in TD-2 (Fig. 1B) revealed a homozygous nucleotide change of A to G at nucleotide 1864 of SEQ ID NO: 2 in exon 13 (Fig. 5A), resulting in a substitution of arginine for glutamine at residue 597 of SEQ ID NO: 1 (Fig. 5B), occurring just proximal to the first predicted transmembrane domain of ABC1 (Fig. 8) at a residue conserved in mouse and as well as a *C. elegans* homolog. This mutation creates a second *Acil* site within exon 13. Segregation analysis of the mutation in this family revealed complete concordance between the mutation and the low HDL phenotype as predicted (Fig 5C). The proband in TD-2 is homozygous for this mutation, consistent with our expectation of a disease causing mutation in this consanguineous family.

Analysis of FHA families

Linkage analysis and refinement of the minimal genomic region containing the gene for FHA

Data from microsatellite typing of individual family members from the four pedigrees of French Canadian origin were analyzed (Fig. 2). A maximum LOD score of 9.67 at a recombination fraction of 0.0 was detected at D9S277 on chromosome 9q31 (Fig. 3; Table 3). Thereafter, 22 markers were typed in a region spanning 10 cM around this locus in these families (Figs. 2 and 3). The frequency for these markers were estimated from a sample of unrelated and unaffected subjects of French ancestry (Table 2).

TD and FHA have thus far been deemed distinct with separate clinical and biochemical characteristics. Even though the genes for these disorders mapped to the same region, it was uncertain whether FHA and TD were due to mutations in the same gene or, alternatively, due to mutations in genes in a similar region. Refinement of the region containing the gene for FHA was possible by examining haplotype sharing and identification of critical recombination events (Fig. 2). Seven separate meiotic recombination events were seen in these families ("A" through "G" in Figs. 2 and 3), clearly indicating that the minimal genomic region containing the potential disease gene was a region of approximately 4.4 cM genomic DNA spanned by marker D9S1690 and D9S1866 (Figs. 2 and 3). This region is consistent with the results of two point linkage analysis which revealed maximal LOD scores with markers

TABLE 3
Two Point Linkage Analysis in FHA

Marker Locus	LOD Score at recombination fraction						
	0	0.01	0.05	0.10	0.20	0.30	0.40
D9S153	-infini	-2.57	0.51	1.48	1.84	1.48	0.76
D9S176	-infini	1.42	3.07	3.39	3.05	2.22	1.12
D9S1630	-infini	3.11	4.04	4.04	3.33	2.24	0.96
D9S277	9.67	9.51	8.89	8.06	6.29	4.30	2.10
D9S306	5.60	5.51	5.13	4.62	3.55	2.36	1.11
D9S1566	-infini	7.24	7.35	6.87	5.50	3.82	1.91
D9S1784	-infini	9.85	9.76	9.03	7.09	4.78	2.25
D9S172	-infini	2.63	3.00	2.87	2.26	1.50	0.67
D9S1632	-infini	5.20	5.97	5.75	4.59	3.02	1.30
D9S1601	0.14	0.13	0.11	0.09	0.06	0.03	0.01
D9S1677	-infini	7.83	7.90	7.38	5.90	4.08	2.01
D9S279	-infini	3.43	3.80	3.66	3.01	2.12	1.05
D9S275	-infini	2.57	2.98	2.91	2.41	1.69	0.81

Results of pairwise linkage analysis using MLINK. Values correspond to the LOD score for linkage between the disease locus and a marker locus for specified values of the recombination fraction.

D9S277 and D9S306 and essentially excluded the region centromeric to D9S1690 or telomeric to D9S1866. An 8th meiotic recombination event ("H" in Fig. 3) further refined the FHA region to distal to D9S277.

As described herein, the *ABC1* gene mapped within this interval. The overlapping genetic data strongly suggested that FHA may in fact be allelic to TD. Utilization of sets of genetic data from FHA and TD provided a telomeric boundary at D9S1866 (meiotic recombinant) (Fig. 3D) and a centromeric marker at D9S127 based on the homozygosity data of TD-2. This refined the locus to approximately 1 Mb between D9S127 and D9S1866. The *ABC1* gene mapped within this minimal region (Fig. 3E).

Mutation detection in FHA

Mutation assessment of the *ABC1* gene was undertaken in FHA-1 (Fig. 2A). Using primers that spanned overlapping segments of the mRNA we performed RT-PCR analysis and subjected these fragments to mutational analysis. A deletion of three nucleotides is evident in the RT-PCR sequence of FHA-1 III.01 (Fig. 6A), resulting in a loss of nucleotides 2151-2153 of SEQ ID NO: 2 and deletion of a leucine (Δ L693) at amino acid position 693 of SEQ ID NO: 1 (Fig. 6A). This leucine is conserved in mouse and *C. elegans* (Fig. 6B). The alteration was detected in the RT-PCR products as well as in genomic sequence from exon 14 specific amplification. This mutation results in a loss of an *EcoRI* restriction site. Analysis of genomic DNA from the family indicated that the mutation segregated completely with the phenotype of HDL deficiency. The loss of the *EcoRI* site results in a larger fragment being remaining in persons heterozygous for this mutation (Fig. 6C). This mutation maps to the first putative transmembrane domain of ABC1 (Fig. 8) and was not seen in 130 chromosomes from persons of French Canadian descent nor seen in over 400 chromosomes from persons of other Western European ancestry.

A mutation has also been found in patient genomic DNA in pedigree FHA-3 from Quebec. The alteration, a 6 bp deletion of nucleotides 5752-5757 of SEQ ID NO: 2 within exon 41, results in a deletion of amino acids 1893 (Glu) and 1894 (Asp) of SEQ ID NO: 1. The deletion was detected as a double, superimposed, sequence

starting from the point of the deletion (Fig. 6D), and was detected in sequence reads in both directions. The deletion can be detected on 3% agarose or 10% polyacrylamide gels, and segregates with disease in FHA-3. It was not seen in 128 normal chromosomes of French-Canadian origin or in 434 other control chromosomes.

5 Amino acids 1893 and 1894 are in a region of the ABC1 protein that is conserved between human, mouse, and *C. elegans* (Fig. 6E), implying that it is of functional importance.

10 An additional mutation has been found in patient genomic DNA in pedigree FHA-2 from Quebec (Fig. 6F). The alteration, a C to T transition at position 6504 of SEQ ID NO: 2, converts an arginine at position 2144 of SEQ ID NO: 1 to a STOP codon, causing truncation of the last 118 amino acids of the ABC1 protein. This alteration segregates with disease in family FHA-2.

15 A summary of all mutations and polymorphisms found in ABC1 is shown in Fig. 11. Each variant indicated as a mutation segregates with low HDL in its family, and was not seen in several hundred control chromosomes.

Functional relationship between changes in ABC1 transcript levels and cholesterol efflux

20 Antisense approaches were undertaken to decrease the ABC1 transcript and assess the effect of alteration of the transcript on intracellular cholesterol transport. The use of antisense primers to the 5' end of ABC1 clearly resulted in a decrease to approximately 50% of normal RNA levels (Fig. 7A). This would be expected to mimic in part the loss of function due to mutations on one allele, similar to that seen in heterozygotes for TD and patients with FHA. Importantly, reduction in the mRNA
25 for the ABC1 gene resulted in a significant reduction in cellular cholesterol efflux (Fig. 7B), further establishing the role of this protein in reverse cholesterol transport and providing evidence that the mutations detected are likely to constitute loss of function mutations. Furthermore, these data support the functional importance of the first 60 amino acids of the protein. Antisense oligonucleotide AN-6 is directed to the
30 novel start codon 5' to the one indicated in AJ012376.1; this antisense oligonucleotide effectively suppresses efflux.

The above-described results were obtained using the following materials and methods.

Patient selection

5 The probands in TD families had previously been diagnosed as suffering from TD based on clinical and biochemical data. Study subjects with FHA were selected from the Cardiology Clinic of the Clinical Research Institute of Montréal. The main criterion was an HDL-C level <5th percentile for age and gender, with a plasma concentration of triglycerides <95th percentile in the proband and a first-degree
10 relative with the same lipid abnormality. In addition, the patients did not have diabetes.

Biochemical studies

15 Blood was withdrawn in EDTA-containing tubes for plasma lipid, lipoprotein cholesterol, ApoAI, and triglyceride analyses, as well as storage at -80°C. Leukocytes were isolated from the buffy coat for DNA extraction.

 Lipoprotein measurement was performed on fresh plasma as described elsewhere (Rogler et al., Arterioscler. Thromb. Vasc. Biol. 15:683-690, 1995). The laboratory participates and meets the criteria of the Lipid Research Program
20 Standardization Program. Lipids, cholesterol and triglyceride levels were determined in total plasma and plasma at density $d < 1.006$ g/mL (obtained after preparative ultracentrifugation) before and after precipitation with dextran manganese. Apolipoprotein measurement was performed by nephelometry for ApoB and ApoAI.

25 *Linkage analysis*

 Linkage between the trait locus and microsatellite loci was analyzed using the FASTLINK version (4.0 P). FASTLINK/MLINK was used for two-point linkage analysis assuming an autosomal dominant trait with complete penetrance. In FHA and TD heterozygotes, the phenotype was HDL deficiency <5th percentile for age and
30 sex. The disease allele frequency was estimated to be 0.005. Marker allele frequencies were estimated from the genotypes of the founders in the pedigrees using

NEWPREP. Multipoint linkage analysis was carried out using FASTLINK/LINKMAP.

Genomic clone assembly and physical map construction of the 9q31 region

5 Using the Whitehead Institute/MIT Center for Genome Research map as a reference, the genetic markers of interest at 9q31 were identified within YAC contigs. Additional markers that mapped to the approximate 9q31 interval from public databases and the literature were then assayed against the YAC clones by PCR and hybridization analysis. The order of markers was based on their presence or absence
10 in the anchored YAC contigs and later in the BAC contig. Based on the haplotype analysis, the region between D9S277 and D9S306 was targeted for higher resolution physical mapping studies using bacterial artificial chromosomes (BACs). BACs within the region of interest were isolated by hybridization of DNA marker probes and whole YACs to high-density filters containing clones from the RPCI-11 human
15 BAC library (Fig. 3).

Sequence retrieval and alignment

 The human *ABC1* mRNA sequence was retrieved from GenBank using the Entrez nucleotide query (Baxevanis et al., A Practical Guide to the Analysis of Genes
20 and Proteins, eds. Baxevanis, A.D. & Ouellette, B.F.F. 98:120, 1998) as GenBank accession number AJ012376.1. The version of the protein sequence we used as wild-type (normal) was CAA10005.1.

 We identified an additional 60 amino acids in-frame with the previously-believed start methionine (Fig. 9A). Bioinformatic analysis of the additional amino
25 acids indicates the presence of a short stretch of basic amino acid residues, followed by a hydrophobic stretch, then several polar residues. This may represent a leader sequence, or another transmembrane or membrane-associated region of the ABC1 protein. In order to differentiate among the foregoing possibilities, antibodies directed to the region of amino acids 1-60 are raised against and used to determine the
30 physical relationship of amino acids 1-60 in relation to the cell membrane. Other standard methods can also be employed, including, for example, expression of fusion

proteins and cell fractionation.

We also identified six errors in the previously-reported nucleotide sequence (at positions 839, 4738, 5017, 5995, 6557, and 6899 of SEQ ID NO: 2; Fig. 11). Hence, the sequence of the ABC1 polypeptide of Fig. 9A differs from CAA10005.1 as follows: Thr⇒Ile at position 1554; Pro⇒Leu at position 1642; Arg⇒Lys at position 1973; and Pro⇒Leu at position 2167. We also identified 5' and 3' UTR sequence (Figs. 9B - 9E).

The mouse *ABC1* sequence used has accession number X75926. It is very likely that this mouse sequence is incomplete, as it lacks the additional 60 amino acids described herein for human ABC1.

Version 1.7 of ClustalW was used for multiple sequence alignments with BOXSHADE for graphical enhancement (http://www.isrec.isb-sib.ch:8080/software/BOX_form.html) with the default parameter. A *Caenorhabditis elegans* ABC1 orthologue was identified with BLAST (version 2.08) using CAA1005.1 (see above) as a query, with the default parameter except for doing an organism filter for *C. elegans*. The selected protein sequence has accession version number AAC69223.1 with a score of 375, and an E value of 103.

Genomic DNA sequencing

BAC DNA was extracted from bacterial cultures using NucleoBond Plasmid Maxi Kits (Clontech, Palo Alto, CA). For DNA sequencing, a sublibrary was first constructed from each of the BAC DNAs (Rowen et al., Automated DNA Sequencing and Analysis, eds. Adams, M.D., Fields, C. & Venter, J.C., 1994). In brief, the BAC DNA was isolated and randomly sheared by nebulization. The sheared DNA was then size fractionated by agarose gel electrophoresis and fragments above 2 kb were collected, treated with Mung Bean nuclease followed by T4 DNA polymerase and klenow enzyme to ensure blunt-ends, and cloned into *Sma*I-cut M13mp19. Random clones were sequenced with an ABI373 or 377 sequencer and fluorescently labeled primers (Applied BioSystems, Foster City, CA). DNASTar software was used for gel trace analysis and contig assembly. All DNA sequences were examined against available public databases primarily using BLASTn with RepeatMasker (University

of Washington).

Reverse transcription (RT)-PCR amplification and sequence analysis

Total RNA was isolated from the cultured fibroblasts of TD and FHA patients, and reverse transcribed with a CDS primer containing oligo d(T)18 using 250 units of SuperScript II reverse transcriptase (Life Technologies, Inc., Rockville, MD) as described (Zhang et al., J. Biol. Chem. 27:1776-1783, 1996). cDNA was amplified with Taq DNA polymerase using primers derived from the published human *ABC1* cDNA sequence (Luciani et al., Genomics 21:150-159, 1994). Six sets of primer pairs were designed to amplify each cDNA sample, generating six DNA fragments which are sequentially overlapped covering 135 to 7014 bp of the full-length human *ABC1* cDNA. The nucleotides are numbered according to the order of the published human cDNA sequence (AJ012376.1). Primer pairs (1): 135-158 (f) and 1183-1199 (r); (2): 1080-1107 (f) and 2247-2273 (r); (3): 2171-2197 (f) and 3376-3404 (r); (4): 3323-3353 (f) and 4587-4617 (r); (5) 4515-4539 (f) and 5782-5811 (r); (6): 5742-5769 (f) and 6985-7014 (r). RT-PCR products were purified by Qiagen spin columns. Sequencing was carried out in a Model 373A Automated DNA sequencer (Applied Biosystems) using Taq di-deoxy terminator cycle sequencing and Big Dye Kits according to the manufacturer's protocol.

Northern blot analysis

Northern transfer and hybridizations were performed essentially as described (Zhang et al., J. Biol. Chem. 27:1776-1783, 1996). Briefly, 20 µg of total fibroblast RNA samples were resolved by electrophoresis in a denaturing agarose (1.2%; w/v) gel in the presence of 7% formaldehyde, and transferred to nylon membranes. The filters were probed with ³²P-labeled human *ABC1* cDNA as indicated. Pre-hybridization and hybridizations were carried out in an ExpressHyb solution (ClonTech) at 68°C according to the manufacturer's protocol.

Detection of the mutations in TD

Genotyping for the T4503C and A1864G variants was performed by PCR

amplification of exon 30 followed by restriction digestion with *HgaI* and amplification of exon 13 followed by digestion with *AciI*, respectively. PCR was carried out in a total volume of 50 μ L with 1.5 mM $MgCl_2$, 187.5 nM of each dNTP, 2.5U Taq polymerase and 15 pmol of each primer (forward primer in exon 30: 5'-CTG CCA GGC AGG GGA GGA AGA GTG-3' (SEQ ID NO: 4); reverse primer spanning the junction of exon 30 and intron 30: 5'-GAA AGT GAC TCA CTT GTG GAG GA-3' (SEQ ID NO: 5); forward primer in intron 12: 5'-AAA GGG GCT TGG TAA GGG TA-3' (SEQ ID NO: 6); reverse in intron 13: 5'-CAT GCA CAT GCA CAC ACA TA -3' (SEQ ID NO: 7)). Following an initial denaturation of 3 minutes at 95°C, 35 cycles consisting of 95°C 10 seconds, 58°C 30 seconds, 72°C 30 seconds were performed, with a final extension of 10 minutes at 72°C. For detection of the T4503C mutation, 15 μ L of exon 30 PCR product was incubated with 4 U *HgaI* in a total volume of 25 μ L, for 2 hours at 37°C, and the resulting fragments were separated on a 1.5% agarose gel. The presence of the T4503C mutation creates a restriction site for *HgaI*, and thus the 194 bp PCR product will be cut into fragments of 134 and 60 bp in the presence of the T4503C variant, but not in its absence. For detection of the A1864G mutation, 15 μ L of exon 13 PCR products were digested with 8 U *AciI* for three hours at 37°C. Products were separated on 2% agarose gels. The presence of the A1864G mutation creates a second *AciI* site within the PCR product. Thus, the 360 bp PCR product is cleaved into fragments of 215 bp and 145 bp on the wild-type allele, but 185 bp, 145 bp and 30 bp on the mutant allele.

Detection of mutation in FHA

Genotyping for the $\Delta 693$ variant was performed by PCR amplification of exon 14 followed by restriction enzyme digestion with *EaeI*. PCR was carried out in a total volume of 80 μ L with 1.5 mM $MgCl_2$, 187.5 nM of each dNTP, 2.5 U Taq polymerase and 20 pmol of each primer (forward primer in exon 14: 5'-CTT TCT GCG GGT GAT GAG CCG GTC AAT-3' (SEQ ID NO: 8); reverse primer in intron 14: 5'-CCT TAG CCC GTG TTG AGC TA-3' (SEQ ID NO: 9)). Following an initial denaturation of 3 minutes at 95°C, 35 cycles consisting of 95°C 10 seconds, 55°C 30 seconds, 72°C 30 seconds were performed, with a final extension of 10

minutes at 72°C. Twenty microliters of PCR product was incubated with 4 U *Eco*RI in a total volume of 25 µL, for two hours at 37°C, and the fragments were separated on a 2 % agarose gel. The presence of the Δ693 mutation destroys a restriction site for *Eco*RI, and thus the 297 bp PCR product will be cut into fragments of 151 bp, 59 bp, 48 bp and 39 bp in the presence of a wild-type allele, but only fragments of 210 bp, 48 bp and 39 bp in the presence of the deletion.

A 6 bp deletion encompassing nucleotides 5752-5757 (inclusive), was detected in exon 41 in the proband of family FHA-3 by genomic sequencing using primers located within the introns flanking this exon. Genotyping of this mutation in family FHA-3 and controls was carried out by PCR with forward (5'-CCT GTA AAT GCA AAG CTA TCT CCT CT- 3' (SEQ ID NO: 10)) and reverse primers (5'-CGT CAA CTC CTT GAT TTC TAA GAT GT (SEQ ID NO: 11)) located near the 5' and 3' ends of exon 41, respectively. Each PCR was carried out as for the genotyping of the 693 variant, but with annealing temperature of 58°C. Twenty microliters of PCR product was resolved on 3% agarose or 10% acrylamide gels. The wild type allele was detected as a 117 bp band and the mutant allele as a 111 bp band upon staining with ethidium bromide.

A C to T transition was detected at nucleotide 6504 in genomic DNA of the proband of family FHA-2. It was detectable as a double C and T peak in the genomic sequence of exon 48 of this individual, who is heterozygous for the alteration. This mutation, which creates a STOP codon that results in truncation of the last 118 amino acids of the ABC1 protein, also destroys an *Rsa*I restriction site that is present in the wild type sequence. Genotyping of this mutation in family FHA-2 and controls was carried out by PCR with forward (5'-GGG TTC CCA GGG TTC AGT AT-3') (SEQ ID NO: 12)) and reverse (5'-GAT CAG GAA TTC AAG CAC CAA-3') (SEQ ID NO: 13)) primers directed to the intronic sequences flanking exon 48. PCR was done as for the 693 variant. Fifteen microliters of PCR product was digested with 5 Units of *Rsa*I at 37°C for two hours and the digestion products resolved on 1.5% agarose gels. The mutant allele is detected as an uncut 436 bp band. The normal sequence is cut by *Rsa*I to produce 332 and 104 bp bands.

Cell culture

Skin fibroblast cultures were established from 3.0 mm punch biopsies of the forearm of FHD patients and healthy control subjects as described (Marcil et al., Arterioscler. Thromb. Vasc. Biol. 19:159-169, 1999).

5

Cellular cholesterol labeling and loading

The protocol for cellular cholesterol efflux experiments was described in detail elsewhere (Marcil et al., Arterioscler. Thromb. Vasc. Biol. 19:159-169, 1999). The cells were ³H-cholesterol labeled during growth and free cholesterol loaded in growth arrest.

10

Cholesterol efflux studies

Efflux studies were carried out from 0 to 24 hours in the presence of purified ApoAI (10 µg protein/mL medium). Efflux was determined as a percent of free cholesterol in the medium after the cells were incubated for specified periods of time. All experiments were performed in triplicate, in the presence of cells from one control subject and the cells from the study subjects to be examined. All results showing an efflux defect were confirmed at least three times.

15

Oligonucleotide synthesis

Eight phosphorothioate deoxyoligonucleotides complementary to various regions of the human *ABCI* cDNA sequence were obtained from GIBCO BRL. The oligonucleotides were purified by HPLC. The sequences of the antisense oligonucleotides and their location are listed. One skilled in the art will recognize that other *ABCI* antisense sequences can also be produced and tested for their ability to decrease *ABCI*-mediated cholesterol regulation.

20

25

30

Name	Sequence (5'-3')	mRNA target	% control
AN-1	GCAGAGGGCATGGCTTTATTTG (SEQ ID NO: 3)	AUG codon	46
AN-2	GTGTTCCCTGCAGAGGGCATG (SEQ ID NO: 30)	AUG codon	50
AN-3	CACTTCCAGTAACAGCTGAC (SEQ ID NO: 31)	5'-Untranslated	79
AN-4	CTTTGCGCATGTCCTTCATGC (SEQ ID NO: 32)	Coding	80

AN-5	GACATCAGCCCTCAGCATCTT (SEQ ID NO: 33)	Coding	120
AN-6:	CAACAAGCCATGTTCCCTC (SEQ ID NO: 34)	Coding	
AN-7:	CATGTTCCCTCAGCCAGC (SEQ ID NO: 35)	Coding	
AN-8:	CAGAGCTCACAGCAGGGA C (SEQ ID NO: 36)	Coding	

5

Cell transfection with antisense oligonucleotides

Cells were grown in 35 mm culture dishes until 80 % confluent, then washed once with DMEM medium (serum and antibiotics free). One milliliter of DMEM (serum and antibiotics free) containing 500 nM antisense oligonucleotides and 5 μ g/ml or 7.5 μ g/ml of lipofectin (GIBCO BRL) were added to each well according to the manufacturer's protocol. The cells were incubated at 37°C for 4 hours, and then the medium was replaced by DMEM containing 10% FCS. Twenty-four hours after the transfection, the total cell RNA was isolated. Ten micrograms of total RNA was resolved on a 1% of agarose-formaldehyde gel and transferred to nylon membrane. The blot was hybridized with α -³²P dCTP labeled human *ABCI* cDNA overnight at 68°C. The membrane was subsequently exposed to x-ray film. The hybridizing bands were scanned by optical densitometry and standard to 28S ribosome RNA.

10

15

Cholesterol efflux with anti-ABCI oligonucleotides

Human skin fibroblasts were plated in 6-well plates. The cells were labeled with ³H-cholesterol (0.2 μ Ci /ml) in DMEM with 10% FBS for two days when the cell reached 50% confluence. The cells were then transfected with the antisense *ABCI* oligonucleotides at 500nM in DMEM (serum and antibiotic free) with 7.5 μ g/ml Lipofectin (GIBCO BRL) according to the manufacturer's protocol. Following the transfection, and the cells were loaded with nonlipoprotein (20 μ g/ml) for 12 hours in DMEM containing 2 mg/ml BSA without serum. The cellular cholesterol pools were then allowed to equilibrate for 6 hours in DMEM-BSA. The cholesterol efflux mediated by ApoAI (10 μ g /ml, in DMEM-BSA) were then carried out which is 48 hours after transfection.

20

25

30

Radiolabeled cholesterol released into the medium is expressed as a percentage of total ³H-cholesterol per well (medium + cell). Results are the mean +/-

SD of triplicate dishes.

Determination of genomic structure of the ABC1 gene

Most splice junction sequences were determined from genomic sequence generated from BAC clones spanning the ABC1 gene. More than 160 kb of genomic sequence were generated. Genomic sequences were aligned with cDNA sequences to identify intron/exon boundaries. In some cases, long distance PCR between adjacent exons was used to amplify intron/exon boundary sequences using amplification primers designed according to the cDNA sequence.

Functionality of the newly-discovered 60 amino acids at the N-terminus

Antisense experiments

Phosphorothioate antisense oligonucleotides were designed to be complementary to the regions of the cDNA near newly discovered translation start site. AN-6 and AN-7 both overlap the initiator methionine codon; this site is in the middle of oligonucleotide AN-6. AN-8 is complementary to the very 5' end of the ABC1 cDNA. Antisense oligonucleotide AN-1 is complementary to the region of the ABC1 cDNA corresponding to the site identified as the ABC1 initiator methionine in AJ012376. Fig. 7C shows that antisense oligonucleotide AN-6 interferes with cellular cholesterol efflux in normal fibroblasts to the same extent as does antisense oligonucleotide AN-1. Transfection with either of these antisense oligonucleotides results in a decrease in cellular cholesterol efflux almost as severe as that seen in FHA cells. In general, antisense oligonucleotides complementary to coding sequences, especially near the 5' end of a gene's coding sequence, are expected to be more effective in decreasing the effective amount of transcript than are oligonucleotides directed to more 3' sequences or to non-coding sequences. The observation that AN-6 depresses cellular cholesterol efflux as effectively as AN-1 implies that both of these oligonucleotides are complementary to ABC1 coding sequences, and that the amino terminal 60 amino acids are likely to be contained in ABC1 protein. In contrast, the ineffectiveness of AN-8 shows that it is likely to be outside the protein coding region of the transcript, as predicted by presence of an in-frame stop codon

between the initiator methionine and the region targeted by AN-8.

Antibody experiments

Polyclonal and monoclonal antibodies have been generated using peptides
5 corresponding to discrete portions of the ABC1 amino acid sequence. One of these,
20-amino acid peptide #2 (Pep2: CSVRLSYPPYEQHECHFPNKA (SEQ ID NO: 37),
in which the N-terminal cysteine was added to facilitate conjugation of the peptide)
corresponds to a protein sequence within the 60 amino-terminal amino acids of the
newly-discovered ABC1 protein sequence. The peptide was coupled to the KLH
10 carrier protein and 300 µg injected at three intervals into two Balb/c mice over a four
week period. The spleen was harvested from the mouse with the highest
ELISA-determined immune response to free peptide, and the cells fused to NS-1
myeloma cells by standard monoclonal antibody generation methods. Positive
hybridomas were selected first by ELISA and then further characterized by western
15 blotting using cultured primary human fibroblasts. Monoclonal cell lines producing a
high antibody titre and specifically recognizing the 245 kD human ABC1 protein
were saved. The same size ABC1 protein product was detected by antibodies directed
to four other discrete regions of the same protein. The 245 kD band could be
eliminated in competition experiments with appropriate free peptide, indicating that it
20 represents ABC1 protein (Fig. 13).

The foregoing experiments indicate that ABC1 protein is detected not only by
antibodies corresponding to amino acid sequences within the previously-described
ABC1 amino acid sequence, but also by the Pep2 monoclonal antibody that
recognizes an epitope within the newly-discovered N-terminal 60 amino acids. The
25 N-terminal 60 amino acid region is therefore coding, and is part of the ABC1 protein.

The epitope recognized by the Pep2 monoclonal antibody is also conserved
among human, mouse, and chicken. Liver tissues from these three species employed
in a Western blot produced an ABC1 band of 245 kD when probed with the Pep2
monoclonal antibody. This indicates that the 60 amino acid N-terminal sequence is
30 part of the ABC1 coding sequence in humans, mice, and chickens. Presence of this
region is therefore evolutionarily conserved and likely to be of important functional

significance for the ABC1 protein.

Bioinformatic analyses of ABC1 protein sequences

Transmembrane prediction programs indicate 13 transmembrane (TM) regions, the first one being between amino acids 26 and 42 (http://psort.nibb.ac.jp:8800/psort/helpwww2.html#ealom). The tentative number of TM regions for the threshold 0.5 is 13. (INTEGRAL Likelihood = -7.75 Transmembrane 26-42). The other 12 TM range in value between -0.64 and -12 (full results below). It is therefore very likely that the newly-discovered 60 amino acids contain a TM domain, and that the amino end of ABC1 may be on the opposite side of the membrane than originally thought.

ALOM: TM region allocation

Init position for calculation: 1
 Tentative number of TMs for the threshold 0.5: 13
 INTEGRAL Likelihood = -7.75 Transmembrane 26 - 42
 INTEGRAL Likelihood = -3.98 Transmembrane 640 - 656
 INTEGRAL Likelihood = -8.70 Transmembrane 690 - 706
 INTEGRAL Likelihood = -9.61 Transmembrane 717 - 733
 INTEGRAL Likelihood = -1.44 Transmembrane 749 - 765
 INTEGRAL Likelihood = -0.64 Transmembrane 771 - 787
 INTEGRAL Likelihood = -1.28 Transmembrane 1041 -1057
 INTEGRAL Likelihood = -12.79 Transmembrane 1351 -1367
 INTEGRAL Likelihood = -8.60 Transmembrane 1661 -1677
 INTEGRAL Likelihood = -6.79 Transmembrane 1708 -1724
 INTEGRAL Likelihood = -3.40 Transmembrane 1737 -1753
 INTEGRAL Likelihood = -1.49 Transmembrane 1775 -1791
 INTEGRAL Likelihood = -8.39 Transmembrane 1854 -1870
 PERIPHERAL Likelihood = 0.69 (at 1643)
 ALOM score: -12.79 (number of TMSs: 13)

There does not appear to be an obvious cleaved peptide, so this first 60 amino acid residues are not likely to be cleaved, and are therefore not specifically a signal/targeting sequence. No other signals (e.g., for targeting to specific organelles) are apparent.

Agonists and Antagonists

Useful therapeutic compounds include those which modulate the expression, activity, or stability of ABC1. To isolate such compounds, ABC1 expression,

biological activity, or regulated catabolism is measured following the addition of candidate compounds to a culture medium of ABC1-expressing cells. Alternatively, the candidate compounds may be directly administered to animals (for example mice, pigs, or chickens) and used to screen for their effects on ABC1 expression.

5 In addition its role in the regulation of cholesterol, ABC1 also participates in other biological processes for which the development of ABC1 modulators would be useful. In one example, ABC1 transports interleukin-1 β (IL-1 β) across the cell membrane and out of cells. IL-1 β is a precursor of the inflammatory response and, as such, inhibitors or antagonists of ABC1 expression or biological activity may be
10 useful in the treatment of any inflammatory disorders, including but not limited to rheumatoid arthritis, systemic lupus erythematosus (SLE), hypo- or hyper- thyroidism, inflammatory bowel disease, and diabetes mellitus. In another example, ABC1 expressed in macrophages has been shown to be engaged in the engulfment and clearance of dead cells. The ability of macrophages to ingest these apoptotic bodies is
15 impaired after antibody-mediated blockade of ABC1. Accordingly, compounds that modulate ABC1 expression, stability, or biological activity would be useful for the treatment of these disorders.

ABC1 expression is measured, for example, by standard Northern blot analysis using an *ABC1* nucleic acid sequence (or fragment thereof) as a hybridization
20 probe, or by Western blot using an anti-ABC1 antibody and standard techniques. The level of ABC1 expression in the presence of the candidate molecule is compared to the level measured for the same cells, in the same culture medium, or in a parallel set of test animals, but in the absence of the candidate molecule. ABC1 activity can also be measured using the cholesterol efflux assay.

25 Transcriptional Regulation of ABC1 Expression

ABC1 mRNA is increased approximately 8-fold upon cholesterol loading. This increase is likely controlled at the transcriptional level. Using the promoter sequence described herein, one can identify transcription factors that bind to the
30 promoter by performing, for example, gel shift assays, DNase protection assays, or *in vitro* or *in vivo* reporter gene-based assays. The identified transcription factors are

themselves drug targets. In the case of ABC1, drug compounds that act through modulation of transcription of ABC1 could be used for HDL modulation, atherosclerosis prevention, and the treatment of cardiovascular disease. For example, using a compound to inhibit a transcription factor that represses ABC1 would be
5 expected to result in up-regulation of ABC1 and, therefore, HDL levels. In another example, a compound that increases transcription factor expression or activity would also increase ABC1 expression and HDL levels.

Transcription factors known to regulate other genes in the regulation of apolipoprotein genes or other cholesterol- or lipid-regulating genes are of particular
10 relevance. Such factors include, but are not limited to, the steroid response element binding proteins (SREBP-1 and SREBP-2), the PPAR (peroxisomal proliferation-activated receptor) transcription factors. Several consensus sites for certain elements are present in the sequenced region 5' to the ABC1 gene (Fig. 16) and are likely to modulate ABC1 expression. For example, PPARs may alter
15 transcription of ABC1 by mechanisms including heterodimerization with retinoid X receptors (RXRs) and then binding to specific proliferator response elements (PPREs). Examples of such PPARs include PPAR α , β , γ and δ . These distinct PPARs have been shown to have transcriptional regulatory effects on different genes. PPAR α is expressed mainly in liver, whereas PPAR γ is expressed in predominantly in
20 adipocytes. Both PPAR α and PPAR γ are found in coronary and carotid artery atherosclerotic plaques and in endothelial cells, smooth muscle cells, monocytes and monocyte-derived macrophages. Activation of PPAR α results in altered lipoprotein metabolism through PPAR α 's effect on genes such as lipoprotein lipase (LPL), apolipoprotein CIII (apo CIII) and apolipoprotein AI (apo AI) and AII (apo AII).
25 PPAR α activation results in overexpression of LPL and apoA-I and apoA-II, but inhibits the expression of apo CIII. PPAR α activation also inhibits inflammation, stimulates lipid oxidation and increases the hepatic uptake and esterification of free fatty acids (FFA's). PPAR α and PPAR γ activation may inhibit nitric oxide (NO) synthase in macrophages and prevent interleukin-1 (IL-1) induced expression of IL-6
30 and cyclo-oxygenase-2 (COX-2) and thrombin induced endothelin-1 expression secondary to negative transcriptional regulation of NF-KB and activation of protein-1

signaling pathway. It has also been shown that PPAR α induces apoptosis in monocyte-derived macrophages through the inhibition of NF-KB activity.

Activation of PPAR α can be achieved by compounds such as fibrates, β -estradiol, arachidonic acid derivatives, WY-14,643 and LTB $_4$ or 8(s)HETE.

5 PPAR γ activation can be achieved through compounds such as thiozolidinedione antidiabetic drugs, 9-HODE and 13-HODE. Additional compounds such as nicotinic acid or HMG CoA reductase inhibitors may also alter the activity of PPARs.

Compounds which alter activity of any of the PPARs (e.g., PPAR α or PPAR γ) may have an effect on ABC1 expression and thereby could affect HDL levels, atherosclerosis and risk of CAD. PPARs are also regulated by fatty acids (including modified fatty acids such as 3 thia fatty acids), leukotrienes such as leukotriene B $_4$ and prostaglandin J $_2$, which is a natural activator/ligand for PPAR γ . Drugs that modulate PPARs may therefore have an important effect on modulating lipid levels (including HDL and triglyceride levels) and altering CAD risk. This effect could be achieved through the modulation of ABC1 gene expression. Drugs may also effect ABC1 gene expression and thereby HDL levels, by an indirect effect on PPARs via other transcriptional factors such as adipocyte differentiation and determination factor-1 (ADD-1) and sterol regulatory element binding protein-1 and 2 (SREBP-1 and 2). Drugs with combined PPAR α and PPAR γ agonist activity or PPAR α and PPAR γ agonists given in combination for example, may increase HDL levels even more.

A PPAR binding site (PPRE element) is found 5' to the ABC1 gene (nucleotides 2150 to 2169 of SEQ ID NO: 14). Like the PPRE elements found in the C-ACS, HD, CYP4A6 and ApoA-I genes, this PPRE site is a trimer related to the PPRE consensus sequence. Partly because of its similarity in the number and arrangement of repeats in this PPAR binding site, this element in particular is very likely to be of physiological relevance to the regulation of the ABC1 gene.

Additional transcription factors which may also have an effect in modulating ABC1 gene expression and thereby HDL levels, atherosclerosis and CAD risk include; REV-ERB α , SREBP-1 & 2, ADD-1, EBP α , CREB binding protein, P300, HNF 4, RAR, LXR, and ROR α . Additional degenerate binding sites for these factors

can be found through examination of the sequence in SEQ ID NO: 14.

Additional utility of ABC1 polypeptides, nucleic acids, and modulators

ABC1 may act as a transporter of toxic proteins or protein fragments (e.g., APP) out of cells. Thus, ABC1 agonists/upregulators may be useful in the treatment of other disease areas, including Alzheimer's disease, Niemann-Pick disease, and Huntington's disease.

ABC transporters have been shown to increase the uptake of long chain fatty acids from the cytosol to peroxisomes and, moreover, to play a role in β -oxidation of very long chain fatty acids. Importantly, in x-linked adrenoleukodystrophy (ALD), fatty acid metabolism is abnormal, due to defects in the peroxisomal ABC transporter. Any agent that upregulates ABC transporter expression or biological activity may therefor be useful for the treatment of ALD or any other lipid disorder.

ABC1 is expressed in macrophages and is required for engulfment of cells undergoing programmed cell death. The apoptotic process itself, and its regulation, have important implications for disorders such as cancer, one mechanism of which is failure of cells to undergo cell death appropriately. ABC1 may facilitate apoptosis, and as such may represent an intervention point for cancer treatment. Increasing ABC1 expression or activity or otherwise up-regulating ABC1 by any method may constitute a treatment for cancer by increasing apoptosis and thus potentially decreasing the aberrant cellular proliferation characterized by this disease. Conversely, down-regulation of ABC1 by any method may provide opportunity for decreasing apoptosis and allowing increased proliferation of cells in conditions where cell growth is limited. Such disorders include but are not limited to neurodeficiencies and neurodegeneration, and growth disorders. ABC1 could, therefore, potentially be used as a method for identification of compounds for use in the treatment of cancer, or in the treatment of degenerative disorders.

Agents that have been shown to inhibit ABC1 include, for example, the anti-diabetic agents glibenclamide and glyburide, flufenamic acid, diphenylamine-2-carbonic acid, sulfobromophthalein, and DIDS.

Agents that upregulate ABC1 expression or biological activity include but are

not limited to protein kinase A, protein kinase C, vanadate, okadaic acid, and IBMX1.

Those in the art will recognize that other compounds can also modulate ABC1 biological activity, and these compounds are also in the spirit of the invention.

5 Drug screens based on the ABC1 gene or protein

 The ABC1 protein and gene can be used in screening assays for identification of compounds which modulate its activity and may be potential drugs to regulate cholesterol levels. Useful ABC1 proteins include wild-type and mutant ABC1 proteins or protein fragments, in a recombinant form or endogenously expressed.

10 Drug screens to identify compounds acting on the ABC1 expression product may employ any functional feature of the protein. In one example, the phosphorylation state or other post-translational modification is monitored as a measure of ABC1 biological activity. ABC1 has ATP binding sites, and thus assays may wholly or in part test the ability of ABC1 to bind ATP or to exhibit ATPase activity. ABC1, by

15 analogy to similar proteins, is thought to be able to form a channel-like structure; drug screening assays could be based upon assaying for the ability of the protein to form a channel, or upon the ability to transport cholesterol or another molecule, or based upon the ability of other proteins bound by or regulated by ABC1 to form a channel. Alternatively, phospholipid or lipid transport can also be used as measures of ABC1

20 biological activity.

 There is evidence that, in addition to its role as a regulator of cholesterol levels, ABC1 also transports anions. Functional assays could be based upon this property, and could employ drug screening technology such as (but not limited to) the ability of various dyes to change color in response to changes in specific ion

25 concentrations in such assays can be performed in vesicles such as liposomes, or adapted to use whole cells.

 Drug screening assays can also be based upon the ability of ABC1 or other ABC transporters to interact with other proteins. Such interacting proteins can be identified by a variety of methods known in the art, including, for example,

30 radioimmunoprecipitation, co-immunoprecipitation, co-purification, and yeast two-hybrid screening. Such interactions can be further assayed by means including but

not limited to fluorescence polarization or scintillation proximity methods. Drug screens can also be based upon functions of the ABC1 protein deduced upon X-ray crystallography of the protein and comparison of its 3-D structure to that of proteins with known functions. Such a crystal structure has been determined for the
5 prokaryotic ABC family member HisP, histidine permease. Drug screens can be based upon a function or feature apparent upon creation of a transgenic or knockout mouse, or upon overexpression of the protein or protein fragment in mammalian cells *in vitro*. Moreover, expression of mammalian (e.g., human) ABC1 in yeast or *C. elegans* allows for screening of candidate compounds in wild-type and mutant
10 backgrounds, as well as screens for mutations that enhance or suppress an ABC1-dependent phenotype. Modifier screens can also be performed in ABC1 transgenic or knock-out mice.

Additionally, drug screening assays can also be based upon ABC1 functions deduced upon antisense interference with the gene function. Intracellular localization
15 of ABC1, or effects which occur upon a change in intracellular localization of the protein, can also be used as an assay for drug screening. Immunocytochemical methods will be used to determine the exact location of the ABC1 protein.

Human and rodent ABC1 protein can be used as an antigen to raise antibodies, including monoclonal antibodies. Such antibodies will be useful for a wide variety of
20 purposes, including but not limited to functional studies and the development of drug screening assays and diagnostics. Monitoring the influence of agents (e.g., drugs, compounds) on the expression or biological activity of ABC1 can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase ABC1 gene
25 expression, protein levels, or biological activity can be monitored in clinical trials of subjects exhibiting altered ABC1 gene expression, protein levels, or biological activity. Alternatively, the effectiveness of an agent determined by a screening assay to modulate ABC1 gene expression, protein levels, or biological activity can be monitored in clinical trials of subjects exhibiting decreased altered gene expression,
30 protein levels, or biological activity. In such clinical trials, the expression or activity of ABC1 and, preferably, other genes that have been implicated in, for example,

cardiovascular disease can be used to ascertain the effectiveness of a particular drug.

For example, and not by way of limitation, genes, including ABC1, that are modulated in cells by treatment with an agent (e.g., compound, drug or small molecule) that modulates ABC1 biological activity (e.g., identified in a screening
5 assay as described herein) can be identified. Thus, to study the effect of agents on cholesterol levels or cardiovascular disease, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of ABC1 and other genes implicated in the disorder. The levels of gene expression can be quantified by Northern blot analysis or RT-PCR, or, alternatively, by measuring the
10 amount of protein produced, by one of a number of methods known in the art, or by measuring the levels of biological activity of ABC1 or other genes. In this way, the gene expression can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during, treatment of the individual with the agent.

15 In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of
20 the agent; (ii) detecting the level of expression of an ABC1 protein, mRNA, or genomic DNA in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the ABC1 protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the ABC1 protein,
25 mRNA, or genomic DNA in the pre-administration sample with the ABC1 protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of ABC1 to higher levels than detected, i.e., to increase the effectiveness of
30 the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of ABC1 to lower levels than detected.

The *ABC1* gene or a fragment thereof can be used as a tool to express the protein in an appropriate cell *in vitro* or *in vivo* (gene therapy), or can be cloned into expression vectors which can be used to produce large enough amounts of ABC1 protein to use in *in vitro* assays for drug screening. Expression systems which may be employed include baculovirus, herpes virus, adenovirus, adeno-associated virus, bacterial systems, and eucaryotic systems such as CHO cells. Naked DNA and DNA-liposome complexes can also be used.

Assays of ABC1 activity includes binding to intracellular interacting proteins; interaction with a protein that up-regulates ABC1 activity; interaction with HDL particles or constituents; interaction with other proteins which facilitate interaction with HDL or its constituents; and measurement of cholesterol efflux. Furthermore, assays may be based upon the molecular dynamics of macromolecules, metabolites and ions by means of fluorescent-protein biosensors. Alternatively, the effect of candidate modulators on expression or activity may be measured at the level of ABC1 protein production using the same general approach in combination with standard immunological detection techniques, such as Western blotting or immunoprecipitation with an ABC1-specific antibody. Again, useful cholesterol-regulating or anti-CVD therapeutic modulators are identified as those which produce an change in ABC1 polypeptide production. Agonists may also affect ABC1 activity without any effect on expression level.

Candidate modulators may be purified (or substantially purified) molecules or may be one component of a mixture of compounds (*e.g.*, an extract or supernatant obtained from cells). In a mixed compound assay, ABC1 expression is tested against progressively smaller subsets of the candidate compound pool (*e.g.*, produced by standard purification techniques, *e.g.*, HPLC or FPLC; Ausubel et al.) until a single compound or minimal compound mixture is demonstrated to modulate ABC1 expression.

Agonists, antagonists, or mimetics found to be effective at modulating the level of cellular ABC1 expression or activity may be confirmed as useful in animal models (for example, mice, pigs, rabbits, or chickens). For example, the compound may ameliorate the low HDL levels of mouse or chicken hypoalphalipoproteinemias.

A compound that promotes an increase in ABC1 expression or activity is considered particularly useful in the invention; such a molecule may be used, for example, as a therapeutic to increase the level or activity of native, cellular ABC1 and thereby treat a low HDL condition in an animal (for example, a human).

5 One method for increasing ABC biological activity is to increase the stabilization of the ABC protein or to prevent its degradation. Thus, it would be useful to identify mutations in an ABC polypeptide (e.g., ABC1) that lead to increased protein stability. These mutations can be incorporated into any protein therapy or gene therapy undertaken for the treatment of low HDL-C or any other
10 condition resulting from loss of ABC1 biological activity. Similarly, compounds that increase the stability of a wild-type ABC polypeptide or decrease its catabolism may also be useful for the treatment of low HDL-C or any other condition resulting from loss of ABC1 biological activity. Such mutations and compounds can be identified using the methods described herein.

15 In one example, cells expressing an ABC polypeptide having a mutation are transiently metabolically labeled during translation and the half-life of the ABC polypeptide is determined using standard techniques. Mutations that increase the half-life of an ABC polypeptide are ones that increase ABC protein stability. These mutations can then be assessed for ABC biological activity. They can also be used to
20 identify proteins that affect the stability of ABC1 mRNA or protein. One can then assay for compounds that act on these factors or on the ability of these factors to bind ABC1.

 In another example, cells expressing wild-type ABC polypeptide are transiently metabolically labeled during translation, contacted with a candidate
25 compounds, and the half-life of the ABC polypeptide is determined using standard techniques. Compounds that increase the half-life of an ABC polypeptide are useful compounds in the present invention.

 If desired, treatment with an agonist of the invention may be combined with any other HDL-raising or anti-CVD therapies.

30 It is understood that, while ABC1 is the preferred ABC transporter for the drug screens described herein, other ABC transporters can also be used. The

replacement of ABC1 with another ABC transporter is possible because it is likely that ABC transporter family members, such as ABC2, ABCR, or ABC8 will have a similar mechanism of regulation.

Exemplary assays are described in greater detail below.

5

Protein-based assays

ABC1 polypeptide (purified or unpurified) can be used in an assay to determine its ability to bind another protein (including, but not limited to, proteins found to specifically interact with ABC1). The effect of a compound on that binding is then determined.

10

Protein Interaction Assays

ABC1 protein (or a polypeptide fragment thereof or an epitope-tagged form or fragment thereof) is harvested from a suitable source (e.g., from a prokaryotic expression system, eukaryotic cells, a cell-free system, or by immunoprecipitation from ABC1-expressing cells). The ABC1 polypeptide is then bound to a suitable support (e.g., nitrocellulose or an antibody or a metal agarose column in the case of, for example, a his-tagged form of ABC1). Binding to the support is preferably done under conditions that allow proteins associated with ABC1 polypeptide to remain associated with it. Such conditions may include use of buffers that minimize interference with protein-protein interactions. The binding step can be done in the presence and absence of compounds being tested for their ability to interfere with interactions between ABC1 and other molecules. If desired, other proteins (e.g., a cell lysate) are added, and allowed time to associate with the ABC polypeptide. The immobilized ABC1 polypeptide is then washed to remove proteins or other cell constituents that may be non-specifically associated with it the polypeptide or the support. The immobilized ABC1 polypeptide is then dissociated from its support, and so that proteins bound to it are released (for example, by heating), or, alternatively, associated proteins are released from ABC1 without releasing the ABC1 polypeptide from the support. The released proteins and other cell constituents can be analyzed, for example, by SDS-PAGE gel electrophoresis, Western blotting and detection with

15

20

25

30

specific antibodies, phosphoamino acid analysis, protease digestion, protein sequencing, or isoelectric focusing. Normal and mutant forms of ABC1 can be employed in these assays to gain additional information about which part of ABC1 a given factor is binding to. In addition, when incompletely purified polypeptide is employed, comparison of the normal and mutant forms of the protein can be used to help distinguish true binding proteins.

The foregoing assay can be performed using a purified or semipurified protein or other molecule that is known to interact with ABC1. This assay may include the following steps.

1. Harvest ABC1 protein and couple a suitable fluorescent label to it;
2. Label an interacting protein (or other molecule) with a second, different fluorescent label. Use dyes that will produce different quenching patterns when they are in close proximity to each other vs. when they are physically separate (i.e., dyes that quench each other when they are close together but fluoresce when they are not in close proximity);
3. Expose the interacting molecule to the immobilized ABC1 in the presence or absence of a compound being tested for its ability to interfere with an interaction between the two; and
4. Collect fluorescent readout data.

Another assay is includes Fluorescent Resonance Energy Transfer (FRET) assay. This assay can be performed as follows.

1. Provide ABC1 protein or a suitable polypeptide fragment thereof and couple a suitable FRET donor (e.g., nitro-benzoxadiazole (NBD)) to it;
2. Label an interacting protein (or other molecule) with a FRET acceptor (e.g., rhodamine);
3. Expose the acceptor-labeled interacting molecule to the donor-labeled ABC1 in the presence or absence of a compound being tested for its ability to interfere with an interaction between the two; and
4. Measure fluorescence resonance energy transfer.

Quenching and FRET assays are related. Either one can be applied in a given case, depending on which pair of fluorophores is used in the assay.

Membrane permeability assay

5 The ABC1 protein can also be tested for its effects on membrane permeability. For example, beyond its putative ability to translocate lipids, ABC1 might affect the permeability of membranes to ions. Other related membrane proteins, most notably the cystic fibrosis transmembrane conductance regulator and the sulfonyleurea receptor, are associated with and regulate ion channels.

10 ABC1 or a fragment of ABC1 is incorporated into a synthetic vesicle, or, alternatively, is expressed in a cell and vesicles or other cell sub-structures containing ABC1 are isolated. The ABC1-containing vesicles or cells are loaded with a reporter molecule (such as a fluorescent ion indicator whose fluorescent properties change when it binds a particular ion) that can detect ions (to observe outward movement), or
15 alternatively, the external medium is loaded with such a molecule (to observe inward movement). A molecule which exhibits differential properties when it is inside the vesicle compared to when it is outside the vesicle is preferred. For example, a molecule that has quenching properties when it is at high concentration but not when it is at another low concentration would be suitable. The movement of the charged
20 molecule (either its ability to move or the kinetics of its movement) in the presence or absence of a compound being tested for its ability to affect this process can be determined.

 In another assay, membrane permeability is determined electro-physiologically by measuring ionic influx or efflux mediated by or modulated by
25 ABC1 by standard electrophysiological techniques. A suitable control (e.g., TD cells or a cell line with very low endogenous ABC1 expression) can be used as a control in the assay to determine if the effect observed is specific to cells expressing ABC1.

 In still another assay, uptake of radioactive isotopes into or out of a vesicle can be measured. The vesicles are separated from the extravesicular medium and the
30 radioactivity in the vesicles and in the medium is quantitated and compared.

Nucleic acid-based assays

ABC1 nucleic acid may be used in an assay based on the binding of factors necessary for ABC1 gene transcription. The association between the *ABC1* DNA and the binding factor may be assessed by means of any system that discriminates between protein-bound and non-protein-bound DNA (e.g., a gel retardation assay). The effect of a compound on the binding of a factor to *ABC1* DNA is assessed by means of such an assay. In addition to *in vitro* binding assays, *in vivo* assays in which the regulatory regions of the *ABC1* gene are linked to reporter genes can also be performed.

Assays measuring ABC1 stability

A cell-based or cell-free system can be used to screen for compounds based on their effect on the half-life of *ABC1* mRNA or ABC1 protein. The assay may employ labeled mRNA or protein. Alternatively, *ABC1* mRNA may be detected by means of specifically hybridizing probes or a quantitative PCR assay. Protein can be quantitated, for example, by fluorescent antibody-based methods.

In vitro mRNA stability assay

1. Isolate or produce, by *in vitro* transcription, a suitable quantity of ABC1 mRNA;
2. Label the ABC1 mRNA;
3. Expose aliquots of the mRNA to a cell lysate in the presence or absence of a compound being tested for its ability to modulate *ABC1* mRNA stability;
4. Assess intactness of the remaining mRNA at suitable time points.

In vitro protein stability assay

1. Express a suitable amount of ABC1 protein;
2. Label the protein;
3. Expose aliquots of the labeled protein to a cell lysate in the presence or absence of a compound being tested for its ability to modulate ABC1 protein stability;
4. Assess intactness of the remaining protein at suitable time points

In vivo mRNA or protein stability assay

1. Incubate cells expressing ABC1 mRNA or protein with a tracer (radiolabeled ribonucleotide or radiolabeled amino acid, respectively) for a very brief time period (e.g., five minutes) in the presence or absence of a compound being tested
5 for its effect on mRNA or protein stability;
2. Incubate with unlabeled ribonucleotide or amino acid; and
3. Quantitate the ABC1 mRNA or protein radioactivity at time intervals beginning with the start of step 2 and extending to the time when the radioactivity in ABC1 mRNA or protein has declined by approximately 80%. It is preferable to
10 separate the intact or mostly intact mRNA or protein from its radioactive breakdown products by a means such as gel electrophoresis in order to quantitate the mRNA or protein.

Assays measuring inhibition of dominant negative activity

- 15 Mutant ABC1 polypeptides are likely to have dominant negative activity (i.e., activity that interferes with wild-type ABC1 function). An assay for a compound that can interfere with such a mutant may be based on any method of quantitating normal ABC1 activity in the presence of the mutant. For example, normal ABC1 facilitates cholesterol efflux, and a dominant negative mutant would interfere with this effect.
- 20 The ability of a compound to counteract the effect of a dominant negative mutant may be based on cellular cholesterol efflux, or on any other normal activity of the wild-type ABC1 that was inhibitable by the mutant.

Assays measuring phosphorylation

- 25 The effect of a compound on ABC1 phosphorylation can be assayed by methods that quantitate phosphates on proteins or that assess the phosphorylation state of a specific residue of a ABC1. Such methods include but are not limited to ³²P labelling and immunoprecipitation, detection with antiphosphoamino acid antibodies (e.g., antiphosphoserine antibodies), phosphoamino acid analysis on 2-dimensional
30 TLC plates, and protease digestion fingerprinting of proteins followed by detection of ³²P-labeled fragments.

Assays measuring other post-translational modifications

The effect of a compound on the post-translational modification of ABC1 is based on any method capable of quantitating that particular modification. For example, effects of compounds on glycosylation may be assayed by treating ABC1 with glycosylase and quantitating the amount and nature of carbohydrate released.

Assays measuring ATP binding

The ability of ABC1 to bind ATP provides another assay to screen for compounds that affect ABC1. ATP binding can be quantitated as follows.

1. Provide ABC1 protein at an appropriate level of purity and reconstitute it in a lipid vesicle;
2. Expose the vesicle to a labeled but non-hydrolyzable ATP analog (such as gamma ³⁵S-ATP) in the presence or absence of compounds being tested for their effect on ATP binding. Note that azido-ATP analogs can be used to allow covalent attachment of the azido-ATP to protein (by means of U.V. light), and permit easier quantitation of the amount of ATP bound to the protein.
3. Quantitate the amount of ATP analog associated with ABC1

Assays measuring ATPase activity

Quantitation of the ATPase activity of ABC1 can also be assayed for the effect of compounds on ABC1. This is preferably performed in a cell-free assay so as to separate ABC1 from the many other ATPases in the cell. An ATPase assay may be performed in the presence or absence of membranes, and with or without integration of ABC1 protein into a membrane. If performed in a vesicle-based assay, the ATP hydrolysis products produced or the ATP hydrolyzed may be measured within or outside of the vesicles, or both. Such an assay may be based on disappearance of ATP or appearance of ATP hydrolysis products.

For high-throughput screening, a coupled ATPase assay is preferable. For example, a reaction mixture containing pyruvate kinase and lactate dehydrogenase can be used. The mixture includes phosphoenolpyruvate (PEP), nicotinamide adenine dinucleotide (NAD⁺), and ATP. The ATPase activity of ABC1 generates ADP from

ATP. The ADP is then converted back to ATP as part of the pyruvate kinase reaction. The product, pyruvate, is then converted to lactate. The latter reaction generates a colored quinone (NADH) from a colorless substrate (NAD⁺), and the entire reaction can be monitored by detection of the color change upon formation of NADH. Since
5 ADP is limiting for the pyruvate kinase reaction, this coupled system precisely monitors the ATPase activity of ABC1.

Assays measuring cholesterol efflux

A transport-based assay can be performed *in vivo* or *in vitro*. For example, the
10 assay may be based on any part of the reverse cholesterol transport process that is readily re-created in culture, such as cholesterol or phospholipid efflux. Alternatively, the assay may be based on net cholesterol transport in a whole organism, as assessed by means of a labeled substance (such as cholesterol).

For high throughput, fluorescent lipids can be used to measure
15 ABC1-catalyzed lipid efflux. For phospholipids, a fluorescent precursor, C6-NBD-phosphatidic acid, can be used. This lipid is taken up by cells and dephosphorylated by phosphatidic acid phosphohydrolase. The product, NBD-diglyceride, is then a precursor for synthesis of glycerophospholipids like phosphatidylcholine. The efflux of NBD-phosphatidylcholine can be monitored by
20 detecting fluorescence resonance energy transfer (FRET) of the NBD to a suitable acceptor in the cell culture medium. This acceptor can be rhodamine-labeled phosphatidylethanolamine, a phospholipid that is not readily taken up by cells. The use of short-chain precursors obviates the requirement for the phospholipid transfer protein in the media. For cholesterol, NBD-cholesterol ester can be reconstituted into
25 LDL. The LDL can efficiently deliver this lipid to cells via the LDL receptor pathway. The NBD-cholesterol esters are hydrolyzed in the lysosomes, resulting in NBD-cholesterol that can now be transported back to the plasma membrane and efflux from the cell. The efflux can be monitored by the aforementioned FRET assay in which NBD transfers its fluorescence resonance energy to the
30 rhodamine-phosphatidylethanolamine acceptor.

Animal Model Systems

Compounds identified as having activity in any of the above-described assays are subsequently screened in any available animal model system, including, but not limited to, pigs, rabbits, and WHAM chickens. Test compounds are administered to these animals according to standard methods. Test compounds may also be tested in mice bearing mutations in the *ABC1* gene. Additionally, compounds may be screened for their ability to enhance an interaction between ABC1 and any HDL particle constituent such as ApoAI, ApoAII, or ApoE.

The cholesterol efflux assay as a drug screen

The cholesterol efflux assay measures the ability of cells to transfer cholesterol to an extracellular acceptor molecule and is dependent on ABC1 function. In this procedure, cells are loaded with radiolabeled cholesterol by any of several biochemical pathways (Marcil et al., *Arterioscler. Thromb. Vasc. Biol.* 19:159-169, 1999). Cholesterol efflux is then measured after incubation for various times (typically 0 to 24 hours) in the presence of HDL3 or purified ApoAI. Cholesterol efflux is determined as the percentage of total cholesterol in the culture medium after various times of incubation. ABC1 expression levels and/or biological activity are associated with increased efflux while decreased levels of ABC1 are associated with decreased cholesterol efflux.

This assay can be readily adapted to the format used for drug screening, which may consist of a multi-well (e.g., 96-well) format. Modification of the assay to optimize it for drug screening would include scaling down and streamlining the procedure, modifying the labeling method, using a different cholesterol acceptor, altering the incubation time, and changing the method of calculating cholesterol efflux. In all these cases, the cholesterol efflux assay remains conceptually the same, though experimental modifications may be made. A transgenic mouse overexpressing ABC1 would be expected to have higher than normal HDL levels.

Knock-out mouse model

An animal, such as a mouse, that has had one or both ABC1 alleles inactivated

(e.g., by homologous recombination) is likely to have low HDL-C levels, and thus is a preferred animal model for screening for compounds that raise HDL-C levels. Such an animal can be produced using standard techniques. In addition to the initial screening of test compounds, the animals having mutant ABC1 genes are useful for further testing of efficacy and safety of drugs or agents first identified using one of the other screening methods described herein. Cells taken from the animal and placed in culture can also be exposed to test compounds. HDL-C levels can be measured using standard techniques, such as those described herein.

WHAM chickens: an animal model for low HDL cholesterol

Wisconsin Hypo-Alpha Mutant (WHAM) chickens arose by spontaneous mutation in a closed flock. Mutant chickens came to attention through their a Z-linked white shank and white beak phenotype referred to as 'recessive white skin' (McGibbon, 1981) and were subsequently found to have a profound deficiency of HDL (Poernama *et al.*, 1990).

This chicken low HDL locus (Y) is Z-linked, or sex-linked. (In birds, females are ZW and males are ZZ). Genetic mapping placed the Y locus on the long arm of the Z chromosome (Bitgood, 1985), proximal to the ID locus (Bitgood, 1988). Examination of current public mapping data for the chicken genome mapping project, ChickMap (maintained by the Roslin Institute; <http://www.ri.bbsrc.ac.uk/chickmap/ChickMapHomePage.html>) showed that a region of synteny with human chromosome 9 lies on the long arm of the chicken Z chromosome (Zq) proximal to the ID locus. Evidence for this region of synteny is the location of the chicken aldolase B locus (ALDOB) within this region. The human ALDOB locus maps to chromosome 9q22.3 (The Genome Database, <http://gdbwww.gdb.org/>), not far from the location of human ABC1. This comparison of maps showed that the chicken Zq region near chicken ALDOB and the human 9q region near human ALDOB represent a region of synteny between human and chicken.

Since a low HDL locus maps to the 9q location in humans and to the Zq region in chickens, these low HDL loci are most probably located within the syntenic region. Thus we predicted that ABC1 is mutated in WHAM chickens. In support of

this, we have identified an E⇒K mutation at a position that corresponds to amino acid 89 of human ABC1 (Figs. 14 and 15). This non-conservative substitution is at a position that is conserved among human, mouse, and chicken, indicating that it is in a region of the protein likely to be of functional importance.

5 Discovery of the WHAM mutation in the amino-terminal portion of the ABC1 protein also establishes the importance of the amino-terminal region. This region may be critical because of association with other proteins required to carry out cholesterol efflux or related tasks. It may be an important regulatory region (there is a phosphorylation site for casein kinase near the mutated residue), or it may help to
10 dictate a precise topological relationship with cellular membranes (the N-terminal 60 amino acid region contains a putative membrane-spanning or membrane-associated segment).

 The amino-terminal region of the protein (up to the first 6-TM region at approximately amino acid 639) is an ideal tool for screening factors that affect ABC1
15 activity. It can be expressed as a truncated protein in ABC1 wild type cells in order to test for interference of the normal ABC1 function by the truncated protein. If the fragment acts in a dominant negative way, it could be used in immunoprecipitations to identify proteins that it may be competing away from the normal endogenous protein.

 The C-terminus also lends itself to such experiments, as do the intracellular
20 portions of the molecule, expressed as fragments or tagged or fusion proteins, in the absence of transmembrane regions.

 Since it is possible that there are several genes in the human genome which affect cholesterol efflux, it is important to establish that any animal model to be used for a human genetic disease represents the homologous locus in that animal, and not a
25 different locus with a similar function. The evidence above establishes that the chicken Y locus and the human chromosome 9 low HDL locus are homologous. WHAM chickens are therefore an important animal model for the identification of drugs that modulate cholesterol efflux.

 The WHAM chickens' HDL deficiency syndrome is not, however, associated
30 with an increased susceptibility to atherosclerosis in chickens. This probably reflects the shorter lifespan of the chicken rather than an inherent difference in the function of

the chicken ABC1 gene compared to the human gene. We propose the WHAM chicken as a model for human low HDL for the development and testing of drugs to raise HDL in humans. Such a model could be employed in several forms, through the use of cells or other derivatives of these chickens, or by the use of the chickens themselves in tests of drug effectiveness, toxicity, and other drug development purposes.

Therapy

Compounds of the invention, including but not limited to, ABC1 polypeptides, ABC1 nucleic acids, other ABC transporters, and any therapeutic agent that modulates biological activity or expression of ABC1 identified using any of the methods disclosed herein, may be administered with a pharmaceutically-acceptable diluent, carrier, or excipient, in unit dosage form. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer such compositions to patients. Although intravenous administration is preferred, any appropriate route of administration may be employed, for example, perenteral, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, or oral administration. Therapeutic formulations may be in the form of liquid solutions or suspension; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

Methods well known in the art for making formulations are found in, for example, Remington: The Science and Practice of Pharmacy, (19th ed.) ed. A.R. Gennaro AR., 1995, Mack Publishing Company, Easton, PA. Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for agonists of the invention include ethylenevinyl acetate

copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, or example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

Compounds

In general, novel drugs for the treatment of aberrant cholesterol levels and/or CVD are identified from large libraries of both natural product or synthetic (or semi-synthetic) extracts or chemical libraries according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening procedure(s) of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using the exemplary methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as modification of existing compounds. Numerous methods are also available for generating random or directed synthesis (*e.g.*, semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available from Brandon Associates (Merrimack, NH) and Aldrich Chemical (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceanographics Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries are produced, if desired, according to methods known in the art, *e.g.*, by standard extraction and fractionation methods. Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (*e.g.*, taxonomic dereplication, biological

dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their HDL-raising and anti-CVD activities should be employed whenever possible.

When a crude extract is found to have cholesterol-modulating or anti-CVD activities or both, further fractionation of the positive lead extract is necessary to isolate chemical constituent responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract having cholesterol-modulating or anti-CVD activities. The same *in vivo* and *in vitro* assays described herein for the detection of activities in mixtures of compounds can be used to purify the active component and to test derivatives thereof. Methods of fractionation and purification of such heterogeneous extracts are known in the art. If desired, compounds shown to be useful agents for the treatment of pathogenicity are chemically modified according to methods known in the art. Compounds identified as being of therapeutic value are subsequently analyzed using any standard animal model of diabetes or obesity known in the art.

It is understood that compounds that modulate activity of proteins that modulate or are modulated by ABC1 are useful compounds for modulating cholesterol levels. Exemplary compounds are provided herein; others are known in the art.

Compounds that are structurally related to cholesterol, or that mimic ApoAI or a related apolipoprotein, and increase ABC1 biological activity are particularly useful compounds in the invention. Other compounds, known to act on the MDR protein, can also be used or derivatized and assayed for their ability to increase ABC1 biological activity. Exemplary MDR modulators are PSC833, bromocriptine, and cyclosporin A.

Screening patients having low HDL-C

ABC1 expression, biological activity, and mutational analysis can each serve as a diagnostic tool for low HDL; thus determination of the genetic subtyping of the *ABC1* gene sequence can be used to subtype low HDL individuals or families to

determine whether the low HDL phenotype is related to ABC1 function. This diagnostic process can lead to the tailoring of drug treatments according to patient genotype, including prediction of side effects upon administration of HDL increasing drugs (referred to herein as pharmacogenomics). Pharmacogenomics allows for the selection of agents (e.g., drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (e.g., the genotype of the individual is examined to determine the ability of the individual to respond to a particular agent).

Agents, or modulators which have a stimulatory or inhibitory effect on ABC1 biological activity or gene expression can be administered to individuals to treat disorders (e.g., cardiovascular disease or low HDL cholesterol) associated with aberrant ABC1 activity. In conjunction with such treatment, the pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in efficacy of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (e.g., drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the activity of ABC1 protein, expression of ABC1 nucleic acid, or mutation content of ABC1 genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons (Eichelbaum, M., Clin. Exp. Pharmacol. Physiol., 23:983-985, 1996; Linder, M. W., Clin. Chem., 43:254-266, 1997). In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). Altered drug action may occur in a patient having a polymorphism

(e.g., an single nucleotide polymorphism or SNP) in promoter, intronic, or exonic sequences of ABC1. Thus by determining the presence and prevalence of polymorphisms allow for prediction of a patient's response to a particular therapeutic agent. In particular, polymorphisms in the promoter region may be critical in determining the risk of HDL deficiency and CVD.

In addition to the mutations in the *ABC1* gene described herein, we have detected polymorphisms in the human *ABC1* gene (Fig. 11). These polymorphisms are located in promoter, intronic, and exonic sequence of ABC1. Using standard methods, such as direct sequencing, PCR, SSCP, or any other polymorphism-detection system, one could easily ascertain whether these polymorphisms are present in a patient prior to the establishment of a drug treatment regimen for a patient having low HDL, cardiovascular disease, or any other ABC1-mediated condition. It is possible that some these polymorphisms are, in fact, weak mutations. Individuals harboring such mutations may have an increased risk for cardiovascular disease; thus, these polymorphisms may also be useful in diagnostic assays.

Association Studies of ABC1 Gene Variants and HDL Levels or Cardiovascular Disease

The following polymorphisms have been examined for their effect on cholesterol regulation and the predisposition for the development of cardiovascular disease.

Substitution of G for A at nucleotide -1045 [G(-1045)A]. This variant is in complete linkage disequilibrium with the variant at -738 in the individuals we have sequenced, and thus any potential phenotypic effects currently attributed to the variant at -738 may at least in part be due to changes at this site.

Substitution of G for A at nucleotide -738 [G(-738)A]. This variant has been found at very high frequencies in populations selected for low HDL cholesterol or premature coronary artery disease.

Insertion of a G nucleotide at position -4 [G ins (-4)]. This variant has been associated with less coronary artery disease in its carriers than in non-carriers.

Substitution of a C for G at nucleotide -57 [G(-57)C]. This variant is in

complete linkage disequilibrium with the variant at -4 in the individuals we have sequenced, and thus the phenotypic effects currently attributed to the variant at -4 may at least in part be due to changes at this site.

5 *Substitution of A for G at nucleotide 730 (R219K).* We have found carriers to have significantly less cardiovascular disease.

Substitution of C for T at nucleotide 1270 (V399A). Within the French Canadian population, this variant has only been found in individuals from the low HDL population. It has also been seen in individuals with low HDL or premature coronary artery disease in individuals of Dutch ancestry.

10 *Substitution of A for G at nucleotide 2385 (V771M).* This variant has been found at an increased frequency in a Dutch population selected for low HDL and at an increased frequency in a population selected for premature coronary artery disease compared to a control Dutch population, indicating carriers of this variant may have reduced HDL and an increased susceptibility to coronary artery disease.

15 *Substitution of C for A at nucleotide 2394 (T774P).* This variant has been seen at lower frequencies in populations with coronary artery disease or low HDL than in individuals without.

Substitution of C for G at nucleotide 2402 (K776N). This variant has been found at a significantly lower frequency (0.56% vs. 2.91%, $p=0.02$) in a coronary artery disease population vs. a control population of similar Dutch background.

20 *Substitution of C for G at nucleotide 3590 (E1172D).* This variant is seen at lower frequencies in individuals with low HDL and in some populations with premature coronary artery disease.

Substitution of A for G at nucleotide 4384 (R1587K). This variant has been found at decreased frequencies in the 1/3 of individuals with the highest HDL levels in our large Dutch coronary artery disease population ($p=0.036$), at increased frequencies in those with HDL cholesterol <0.9 mmol/L ($p<0.0001$) and at decreased frequencies in the cohorts with HDL cholesterol >1.4 mmol/L in both this population ($p=0.02$) and the Dutch control population ($p=0.003$).

30 *Substitution of G for C at nucleotide 5266 (S1731C).* Two FHA individuals who have this variant on the other allele have much lower HDL cholesterol

(0.155 ± 0.025) than the FHA individuals in the family who do not have this variant on the other allele (0.64 ± 0.14 , $p=0.0009$). This variant has also been found in one general population French Canadian control with HDL at the 8th percentile (0.92) and one French Canadian individual from a population selected for low HDL and coronary disease (0.72).

Substitution of G for A at nucleotide -1113 [A(-1113)G]. This variant has been seen at varying frequencies in populations distinguished by their HDL levels.

Additional polymorphisms that may be associated with altered risk for cardiovascular disease or altered cholesterol levels are as follows:

Substitution of G for A at nucleotide 2723 (I883M). This variant has been seen at a much higher frequency in individuals of Dutch ancestry with premature coronary artery disease.

Insertion of 4 nucleotides (CCCT) at position -1181.

Substitution of C for A at nucleotide -479 (linkage disequilibrium with -518).

Substitution of G for A at nucleotide -380.

Other Embodiments

All publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication was specifically and individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations following, in general, the principles of the invention and including such departures from the present disclosure within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth.

What we claim is:

1. A substantially pure ABC1 polypeptide having ABC1 biological activity.
- 5 2. The substantially pure ABC1 polypeptide of claim 1, wherein said ABC1 polypeptide is human ABC1.
3. The substantially pure ABC1 polypeptide of claim 1, wherein said polypeptide comprises amino acids 1 to 60 of SEQ ID NO: 1.
- 10 4. The substantially pure ABC1 polypeptide of claim 1, wherein said polypeptide comprises amino acids 61 to 2261 of SEQ ID NO: 1.
5. The substantially pure ABC1 polypeptide of claim 1, wherein said polypeptide comprises amino acids 1 to 2261 of SEQ ID NO: 1.
- 15 6. A substantially pure ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 1.
7. A substantially pure ABC1 polypeptide comprising amino acids 61 to 2261 of SEQ ID NO: 1.
- 20 8. A substantially pure ABC1 polypeptide comprising amino acids 1 to 2261 of SEQ ID NO: 1.
- 25 9. A substantially pure nucleic acid molecule that hybridizes at high stringency conditions to nucleotides 75 to 254 of SEQ ID NO: 2 and encodes a polypeptide having ABC1 biological activity.
- 30 10. A substantially pure nucleic acid molecule encoding an ABC1 polypeptide having ABC1 biological activity.

11. The substantially pure nucleic acid molecule of claim 9 or 10, wherein said nucleic acid molecule comprises nucleotides 75 to 254 of SEQ ID NO: 2.

5 12. The substantially pure nucleic acid molecule of claim 9 or 10, wherein said nucleic acid molecule comprises nucleotides 255 to 6857 of SEQ ID NO: 2.

13. The substantially pure nucleic acid molecule of claim 9 or 10, wherein said nucleic acid molecule comprises nucleotides 75 to 6857 of SEQ ID NO: 2.

10 14. An expression vector comprising the nucleic acid molecule of claim 9.

15. A cell expressing the nucleic acid molecule of claim 9.

16. A non-human mammal expressing the nucleic acid molecule of claim 9.

15 17. A substantially pure nucleic acid molecule comprising nucleotides 75 to 254 of SEQ ID NO: 2.

20 18. A substantially pure nucleic acid molecule comprising nucleotides 255 to 6857 of SEQ ID NO: 2.

19. A substantially pure nucleic acid molecule comprising nucleotides 75 to 6857 of SEQ ID NO: 2.

25 20. A substantially pure nucleic acid molecule comprising at least thirty consecutive nucleotides corresponding to nucleotides 7015-7860 of SEQ ID NO: 2.

30 21. The substantially pure nucleic acid molecule of claim 20, wherein said nucleic acid molecule comprises nucleotides 7015-7860 of SEQ ID NO: 2.

22. A substantially pure nucleic acid molecule that hybridizes at high stringency to a probe comprising nucleotides 7015-7860 of SEQ ID NO: 2.

5 23. A method of treating a human having low HDL cholesterol or cardiovascular disease, said method comprising administering to said human an ABC1 polypeptide, or cholesterol-regulating fragment thereof.

10 24. The method of claim 23, wherein said ABC1 polypeptide has the sequence of SEQ ID NO: 1.

25. The method of claim 23, wherein said ABC1 polypeptide comprises a mutation that increases its stability.

15 26. The method of claim 23, wherein said ABC1 polypeptide comprises a mutation that increases its biological activity.

20 27. A method of treating a human having low HDL cholesterol or cardiovascular disease, said method comprising administering to said human a nucleic acid molecule encoding an ABC1 polypeptide or a cholesterol-regulating fragment thereof.

28. The method of claim 27, wherein said ABC1 polypeptide has the amino acid sequence of SEQ ID NO: 1.

25 29. The method of claim 27, wherein said ABC1 polypeptide comprises a mutation that increases its stability.

30 30. The method of claim 27, wherein said ABC1 polypeptide comprises a mutation that increases its biological activity.

31. The method of claim 30, wherein said biological activity is regulation of cholesterol.

5 32. The method of claim 27, wherein said human has low HDL cholesterol levels relative to normal.

33. A method of increasing ABC1 biological activity in a human, said method comprising administering to said human a nucleic acid molecule that hybridizes at high stringency conditions to nucleotides 75 to 254 of SEQ ID NO: 2 and encodes a polypeptide having ABC1 biological activity.

10

34. The method of claim 33, wherein said human has a disease selected from the group consisting of Alzheimer's disease, Niemann-Pick disease, Huntington's disease, x-linked adrenoleukodystrophy, and cancer.

15

35. A method of increasing ABC1 biological activity in a human, said method comprising administering to said human a compound that increases ABC1 biological activity.

20 36. The method of claim 35, wherein said human has a disease selected from the group consisting of Alzheimer's disease, Niemann-Pick disease, Huntington's disease, x-linked adrenoleukodystrophy, and cancer.

25 37. A method of preventing cardiovascular disease in a human, said method comprising administering to said human an expression vector comprising an *ABC1* nucleic acid molecule operably linked to a promoter, said *ABC1* nucleic acid molecule encoding an ABC1 polypeptide having ABC1 biological activity.

38. A method of preventing or ameliorating the effects of a disease-causing mutation in an *ABCI* gene in a human, said method comprising introducing into said human an expression vector comprising a promoter operably linked to an *ABCI* nucleic acid molecule encoding an ABC1 polypeptide having ABC1 biological activity.

39. A method of treating or preventing cardiovascular disease in an animal, said method comprising administering to said animal a compound that mimics the activity of wild-type ABC1.

40. The method of claim 39, wherein said animal is a human.

41. A method of treating or preventing cardiovascular disease in an animal, said method comprising administering to said animal a compound that modulates the biological activity of ABC1.

42. The method of claim 41, wherein said animal is a human.

43. The method of claim 41, wherein said compound is selected from a group consisting of protein kinase A, protein kinase C, vanadate, okadaic acid, IBMX1, fibrates, β -estradiol, arachidonic acid derivatives, WY-14,643, LTB4, 8(s)HETE, thiozolidinedione antidiabetic drugs, 9-HODE, 13-HODE, nicotinic acid, HMG CoA reductase inhibitors, and compounds that increase PPAR-mediated ABC1 expression.

44. The method of claim 23, 27, 39, or 41, wherein said cardiovascular disease is coronary artery disease, cerebrovascular disease, coronary restenosis, or peripheral vascular disease.

45. A method for determining whether a candidate compound is useful for modulating cholesterol levels, said method comprising the steps of:

- (a) providing a chicken comprising a mutation in an *ABC1* gene;
 - (b) administering said candidate compound to said chicken; and
 - 5 (c) measuring ABC1 biological activity in said chicken,
- wherein altered ABC1 biological activity, relative to a WHAM chicken not contacted with said compound, indicates that said candidate compound modulates cholesterol levels.

10 46. The method of claim 45, wherein said ABC1 biological activity is transport of cholesterol.

47. A method for determining whether a candidate compound modulates ABC1 biological activity, said method comprising the steps of:

- 15 (a) providing a cell expressing an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 1;
 - (b) contacting said cell with said candidate compound; and
 - (c) measuring ABC1 biological activity of said cell,
- wherein altered ABC1 biological activity, relative to a cell not contacted with said compound, indicates that said candidate compound modulates ABC1 biological activity.

48. A method for determining whether a candidate compound modulates ABC1 expression, said method comprising the steps of:

- 25 (a) providing a cell expressing an *ABC1* gene comprising nucleotides 75 to 254 of SEQ ID NO: 2;
 - (b) contacting said cell with said candidate compound; and
 - (c) measuring ABC1 expression of said cell,
- wherein altered ABC1 expression, relative to a cell not contacted with said compound, indicates that said candidate compound modulates ABC1 expression.

30

49. A method for determining whether a candidate compound modulates ABC1 expression, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising an ABC1 promoter operably linked to a reporter gene;

5 (b) contacting said nucleic acid molecule with said candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said compound, indicates that said candidate compound modulates ABC1 expression.

10 50. The method of claim 49, wherein said promoter comprises 50 consecutive nucleotides selected from nucleotides 1 to 8238 of SEQ ID NO: 14.

51. The method of claim 50, wherein said promoter comprises a binding site for a transcription factor selected from a group consisting of steroid response element
15 binding proteins, peroxisomal proliferation-activated receptors, retinoid X receptors, and RAR-related orphan receptors.

52. A method for determining whether a candidate compound modulates ABC1 biological activity, said method comprising the steps of:

20 (a) providing an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 1;

(b) contacting said polypeptide with said candidate compound; and

(c) measuring ABC1 biological activity,

25 wherein a change in ABC1 biological activity, relative to a control not contacted with said compound, indicates that said candidate compound modulates ABC1 biological activity.

53. A method for determining whether a candidate compound modulates ABC1 expression, said method comprising the steps of:

(a) providing an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 1;

5 (b) contacting said polypeptide with said candidate compound; and

(c) measuring expression of said ABC1 polypeptide, wherein a change in expression of said ABC1 polypeptide, relative to a control not contacted with said compound, indicates that said candidate compound modulates ABC1 expression.

10

54. A method for determining whether candidate compound modulates ABC1 biological activity, said method comprising the steps of:

(a) providing an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 1;

15 (b) contacting said polypeptide with said candidate compound; and

(c) measuring binding of said ABC1 polypeptide to said candidate compound, wherein binding of said ABC1 polypeptide to said compound indicates that said candidate compound modulates ABC1 biological activity.

20 55. A method for determining whether candidate compound modulates ABC1 biological activity, said method comprising the steps of:

(a) providing (i) an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 1, and (ii) a second polypeptide that interacts with said ABC1 polypeptide;

(b) contacting said polypeptides with said candidate compound; and

25 (c) measuring interaction of said ABC1 polypeptide with said second polypeptide, wherein an alteration in the interaction of said ABC1 polypeptide with said second polypeptide indicates that said candidate compound modulates ABC1 biological activity.

30

56. A method for determining whether a candidate compound increases the stability or decreases the regulated catabolism of an ABC1 polypeptide, said method comprising the steps of:

- 5 (a) providing a cell comprising an ABC1 polypeptide comprising amino acids 1 to 60 of SEQ ID NO: 1;
- (b) contacting said cell with said candidate compound; and
- (c) measuring the half-life of said ABC1 polypeptide,
- wherein an increase in said half-life, relative to a control not contacted with said compound, indicates that said candidate compound increases the stability or
- 10 decreases the regulated catabolism of an ABC1 polypeptide.

57. A method for determining whether a candidate compound modulates ABC1 biological activity, said method comprising the steps of:

- 15 (a) providing an ABC1 polypeptide in a lipid membrane;
- (b) contacting said polypeptide with said candidate compound; and
- (c) measuring ABC1-mediated lipid transport across said lipid membrane,
- wherein a change in lipid transport, relative to a control not contacted with said compound, indicates that said candidate compound modulates ABC1 biological activity.

20

58. The method of claim 49, 52, 53, 54, 55, or 57, wherein said ABC1 polypeptide is in a cell-free system.

59. The method of claim 49, 52, 53, 54, 55, or 57, wherein said ABC1

25 polypeptide is in a cell.

60. The method of claim 59, wherein said cell is from a WHAM chicken.

61. The method of claim 59, wherein said cell is in a human or in a non-

30 human mammal.

62. The method of claim 61, wherein said animal is a WHAM chicken.

63. The method of claim 52, wherein said biological activity is transport of lipid or interleukin-1.

5

64. The method of claim 62, wherein said lipid is cholesterol.

65. The method of claim 64, wherein said cholesterol is HDL-cholesterol.

10

66. The method of claim 52, wherein said biological activity is binding or hydrolysis of ATP by the ABC1 polypeptide.

15

67. A method for determining whether a patient has an increased risk for cardiovascular disease, said method comprising determining whether an *ABC1* gene of said patient has a mutation, wherein a mutation indicates that said patient has an increased risk for cardiovascular disease.

20

68. A method for determining whether a patient has an increased risk for cardiovascular disease, said method comprising measuring ABC1 biological activity in said patient or in a cell from said patient, wherein increased or decreased levels in said ABC1 biological activity, relative to normal levels, indicates that said patient has an increased risk for cardiovascular disease.

25

69. A method for determining whether a patient has an increased risk for cardiovascular disease, said method comprising measuring ABC1 expression in said patient or in a cell from said patient, wherein decreased levels in said ABC1 expression relative to normal levels, indicates that said patient has an increased risk for cardiovascular disease.

30

70. The method of claim 69, wherein said ABC1 expression is determined by measuring levels of ABC1 polypeptide.

5 71. The method of claim 69, wherein said ABC1 expression is determined by measuring levels of *ABC1* RNA.

72. A non-human mammal comprising a transgene comprising a nucleic acid molecule encoding a dominant-negative ABC1 polypeptide.

10 73. A cell isolated from a non-human mammal comprising a transgene comprising a nucleic acid molecule encoding an ABC1 polypeptide having biological activity.

15 74. A method for determining whether a candidate compound decreases the inhibition of a dominant-negative ABC1 polypeptide, said method comprising the steps of:

- (a) providing a cell expressing a dominant-negative ABC1 polypeptide;
- (b) contacting said cell with said candidate compound; and
- (c) measuring ABC1 biological activity of said cell,

20 wherein an increase in said ABC1 biological activity, relative to a cell not contacted with said compound, indicates that said candidate compound decreases the inhibition of a dominant-negative ABC1 polypeptide.

25 75. A method for determining whether a person has an altered risk for developing cardiovascular disease, comprising examining the person's ABC1 gene for polymorphisms, wherein the presence of a polymorphism associated with cardiovascular disease indicates the person has an altered risk for developing cardiovascular disease.

30

76. A method for predicting a person's response to a drug, comprising determining whether the person has a polymorphism in an ABC1 gene that alters the person's response to said drug.

5 77. A method for predicting a person's response to a drug, comprising determining whether the person has a polymorphism in an ABC1 promoter that alters the person's response to said drug.

10 78. A method for altering ABC1 expression in a cell, said method comprising contacting said cell with a compound selected from a group consisting of fibrates, β -estradiol, arachidonic acid derivatives, WY-14,643, LTB₄, 8(s)HETE, thiozolidinedione antidiabetic drugs, 9-HODE, 13-HODE, nicotinic acid, HMG CoA reductase inhibitors, and compounds that increase PPAR-mediated ABC1 expression.

15 79. A pharmaceutical composition comprising (i) a nucleic acid molecule that hybridizes under high stringency conditions to nucleotides 75 to 254 of SEQ ID NO: 2 and encodes a polypeptide having ABC1 biological activity; and (ii) a pharmaceutically acceptable carrier.

20 80. A nucleic acid that hybridizes under high stringency conditions to nucleotides 1 to 8236 of SEQ ID NO: 14.

25 81. A nucleic acid comprising a region that is 80% identical to at least thirty contiguous nucleotides of nucleotides 1 to 8236 of SEQ ID NO: 14.

82. A method for determining whether candidate compound modulates ABC1 biological activity, said method comprising the steps of:

(a) providing an ABC1 polypeptide;

(b) contacting said polypeptide with cholesterol and said candidate compound;

5 and

(c) measuring binding of said cholesterol to said ABC1 polypeptide, wherein binding of said cholesterol to said ABC1 polypeptide indicates that said candidate compound modulates ABC1 biological activity.

10 83. The method of claim 82, wherein said cholesterol is HDL cholesterol.

84. The method of claim 82, wherein said method is performed in a cell free assay.

15 85. The method of claim 82, wherein said ABC1 polypeptide comprises amino acids 1 to 60 of SEQ ID NO: 1.

86. the method of claim 82, wherein said cholesterol or said ABC1 polypeptide is detectably labeled.

Family TD - 1

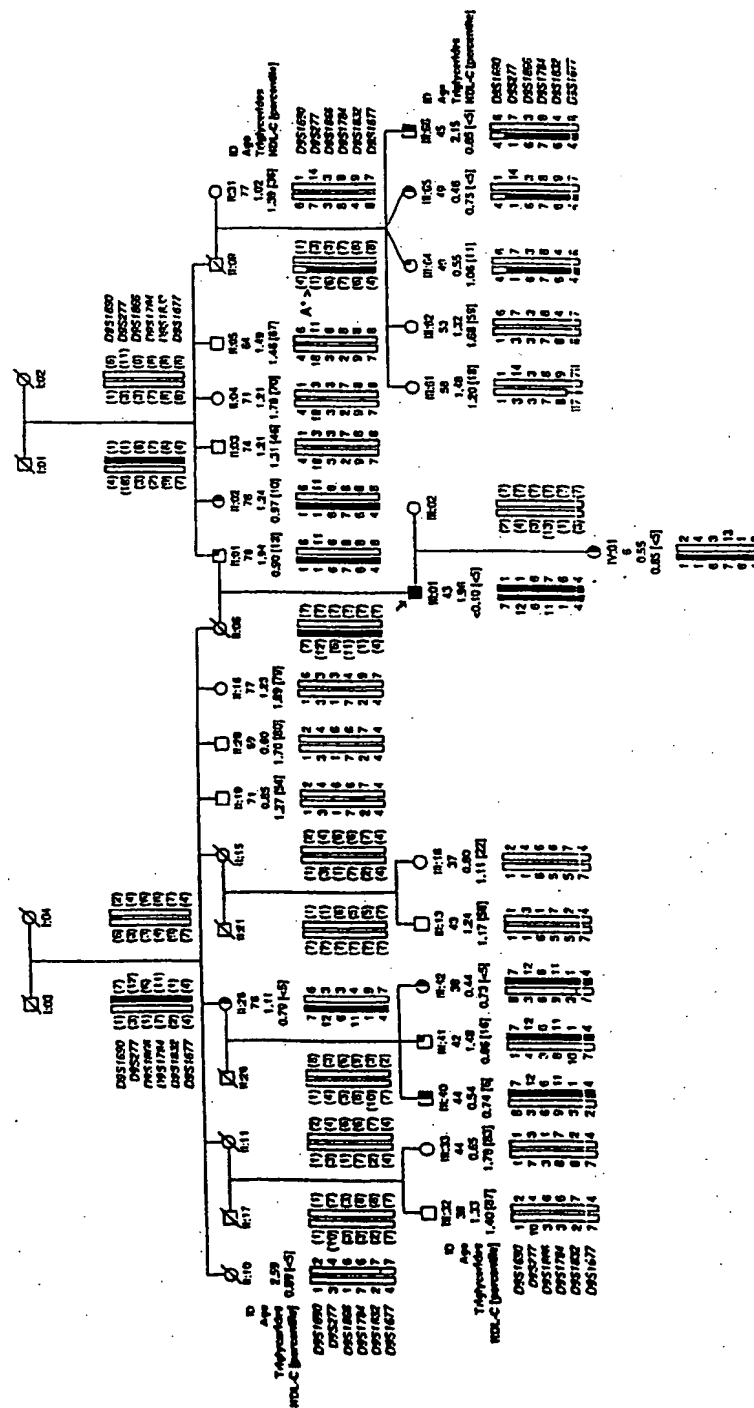
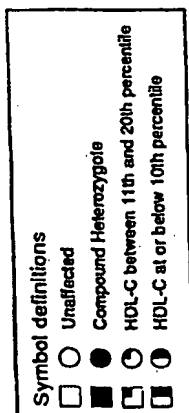


Fig. 1A

Family TD - 2

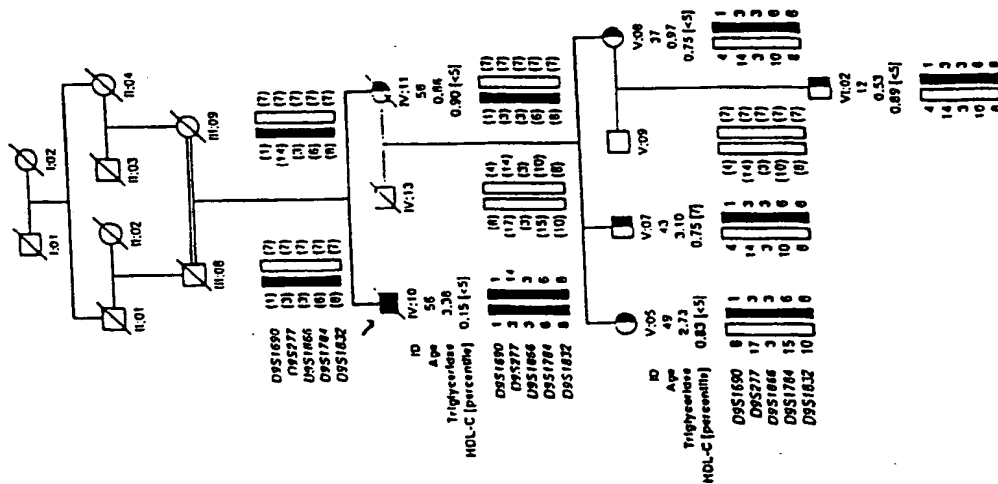


Fig. 13

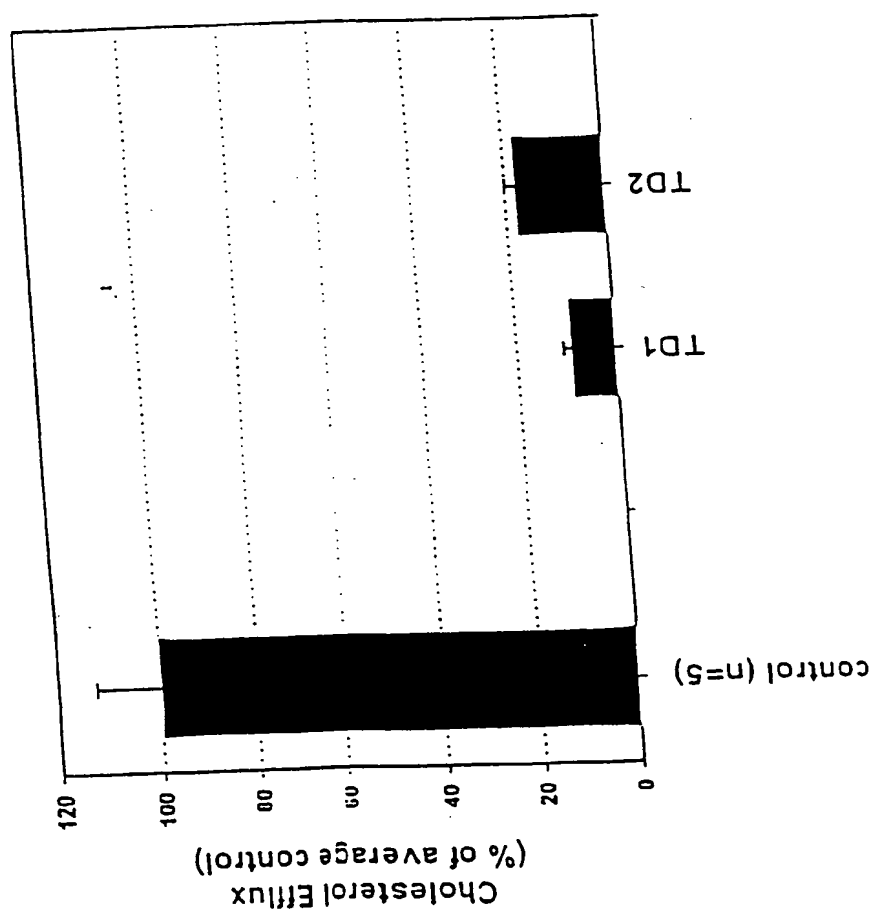
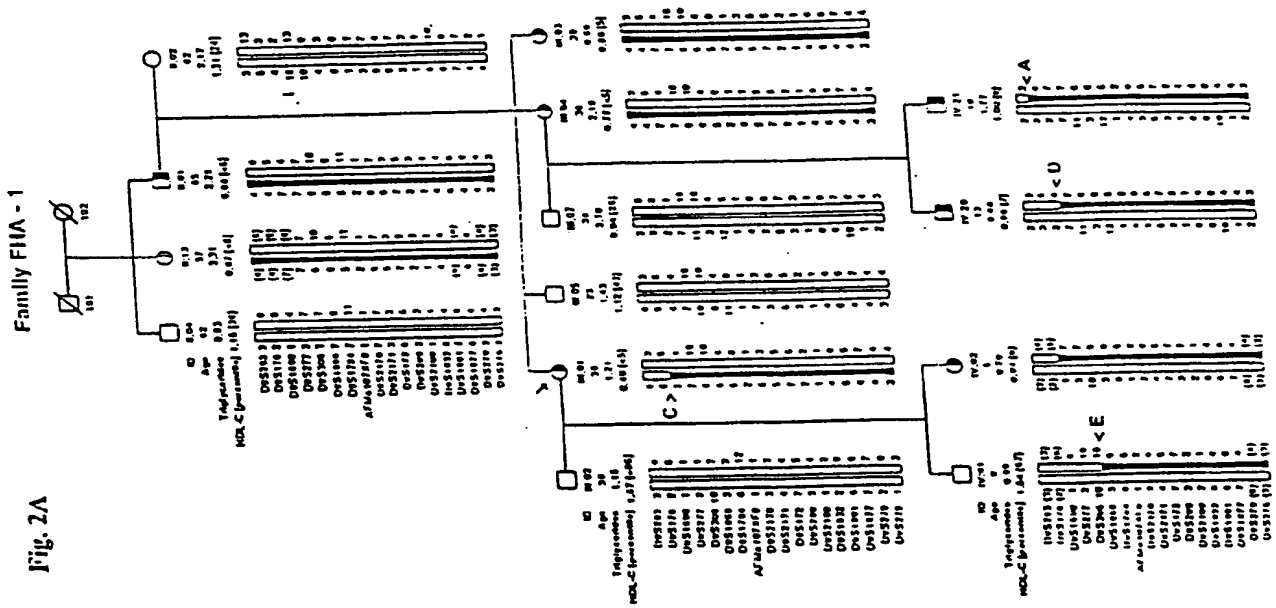


Fig. 1C



Family FIIA - 3

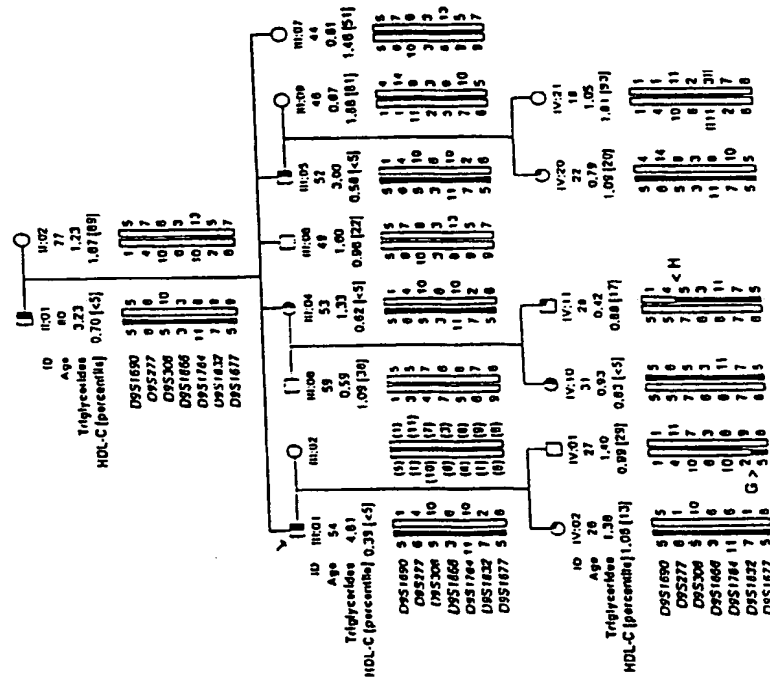
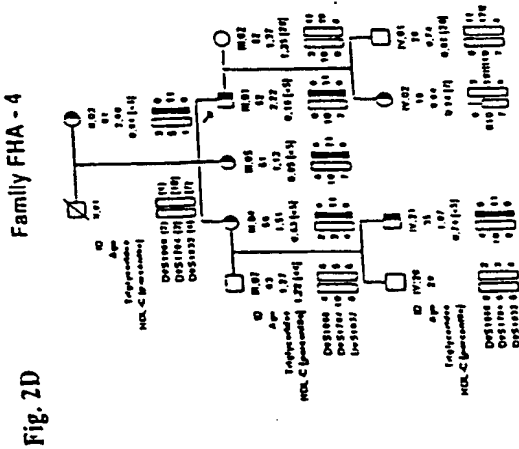


Fig. 2C



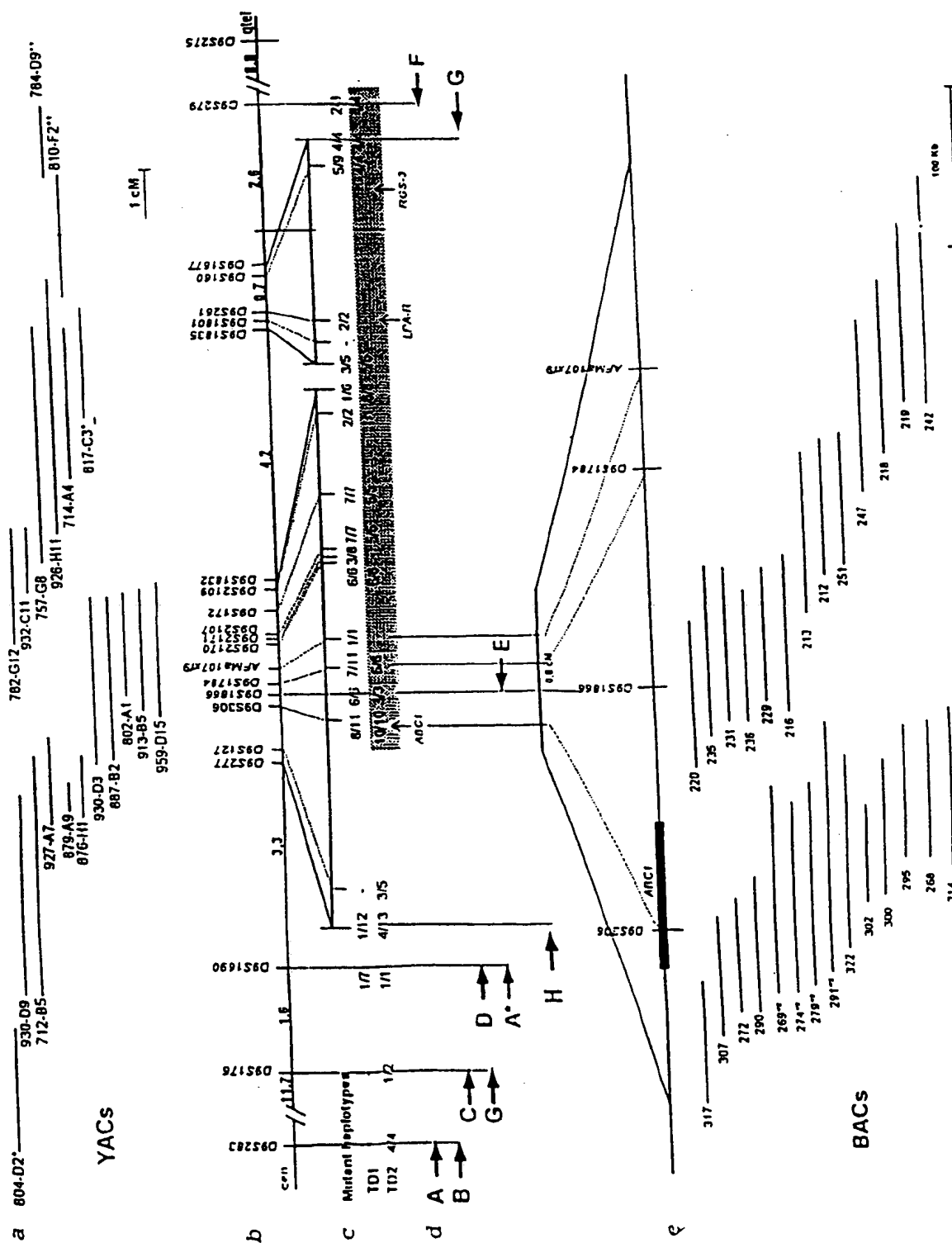


Fig. 3

Exon 30 mutation:

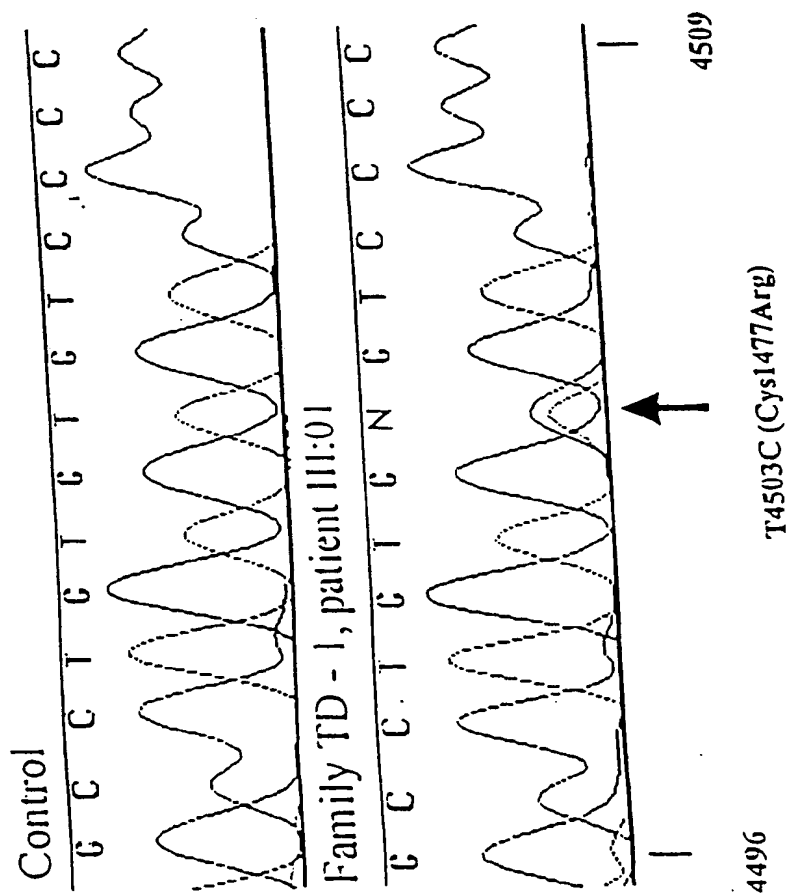


Fig. 4A

Exon 33
TD-1

4485 4503 4529

| | |

wt sequence aagaagatgctgcctgtgTgtccccccaggggcagggggcctgcct

HUMAN_ABC1 R R M L P V C P P G A G G L F

MOUSE_ABC1 R R M L P V C P P G A G G L F

Patient: R R M L P V R P P G A G G L F

CAREL_ABC - - L - - - - - G G S -

Patient: aagaagatgctgcctgtgCgtccccccaggggcagggggcctgcct

Fig. 4B

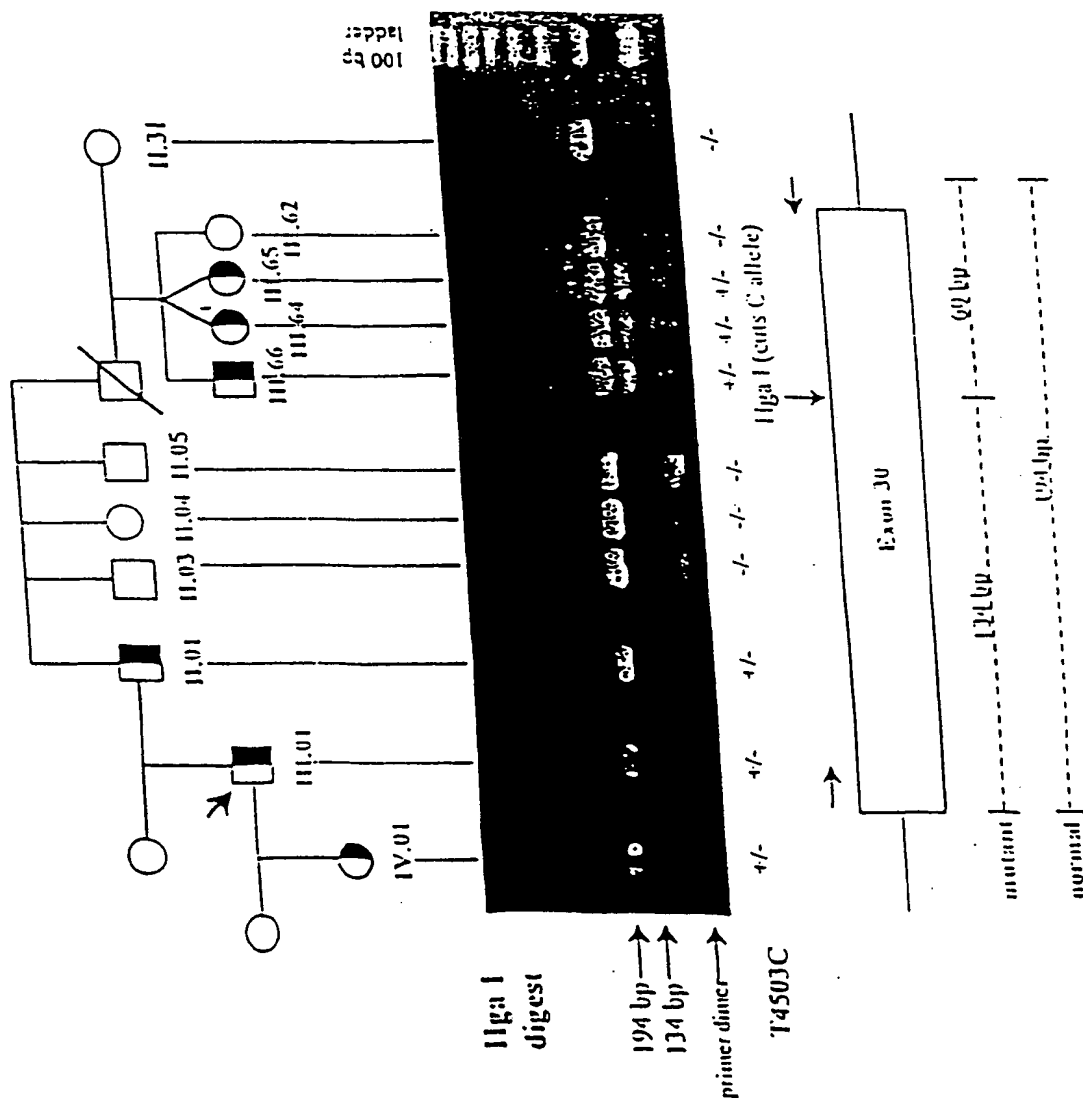


Fig. 4C

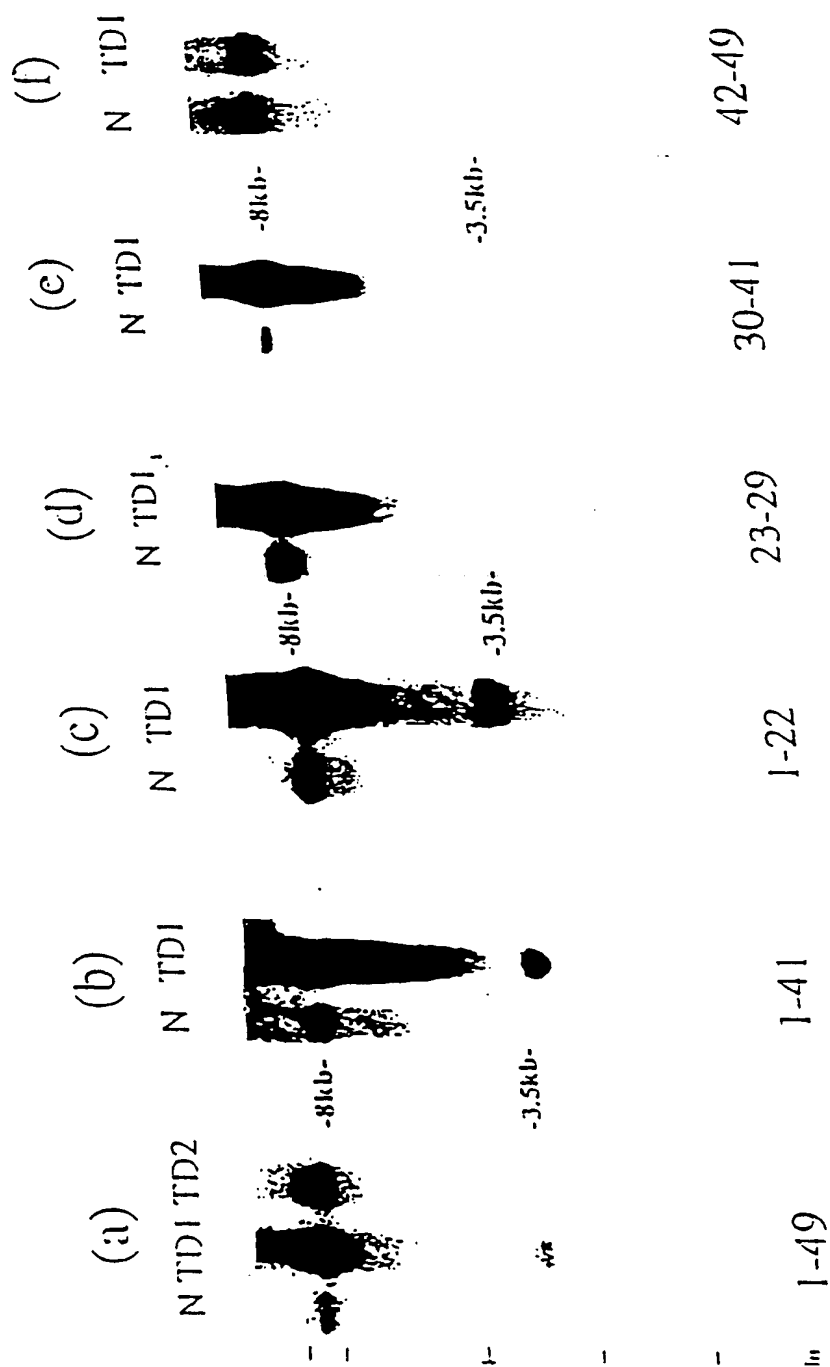


Fig. 4D

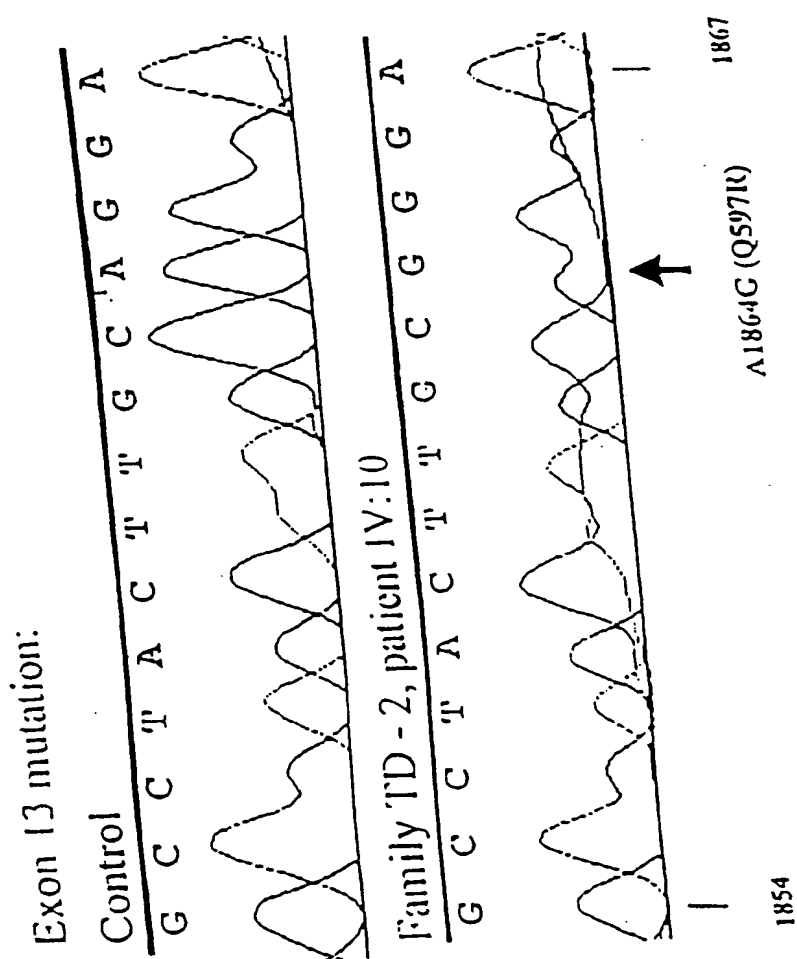
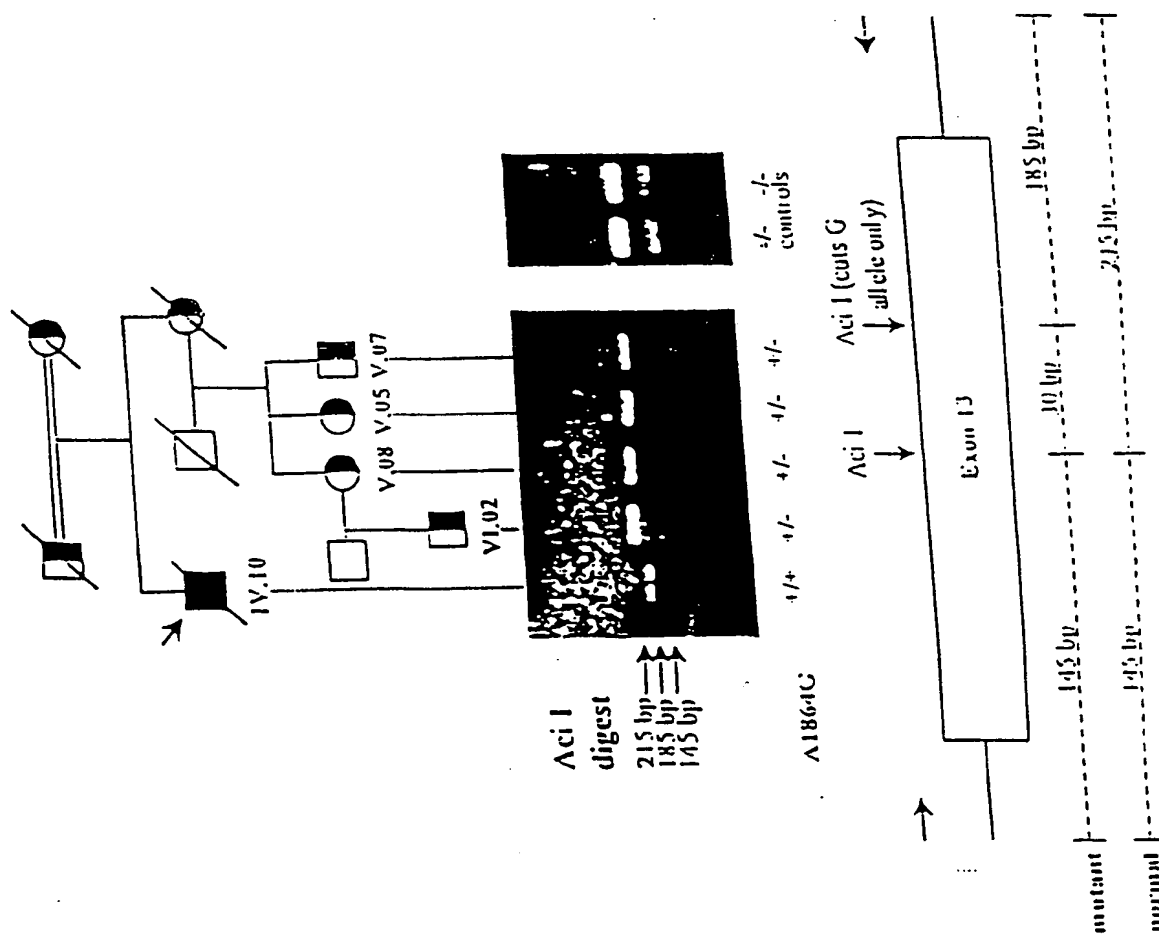


Fig. 5A

Exon 13
TD-1

	1842		1864		1886
wt sequence	tggggggggcttcgcctacttgcaggatgaggagcaggcaatc				
HUMAN_ABC1	M G G F A Y L Q D V V E Q A I				
MOUSE_ABC1	M G G F A Y L Q D V V E Q A I				
Patient	M G G F A Y L R D V V E Q A I				
CASE1_ABC	- - - F H T V Q R A V D V A I				
Patient	tggggggggcttcgcctacttgcaggatgaggagcaggcaatc				

Fig. 5B



Exon 14: FHA - I, patient III:01

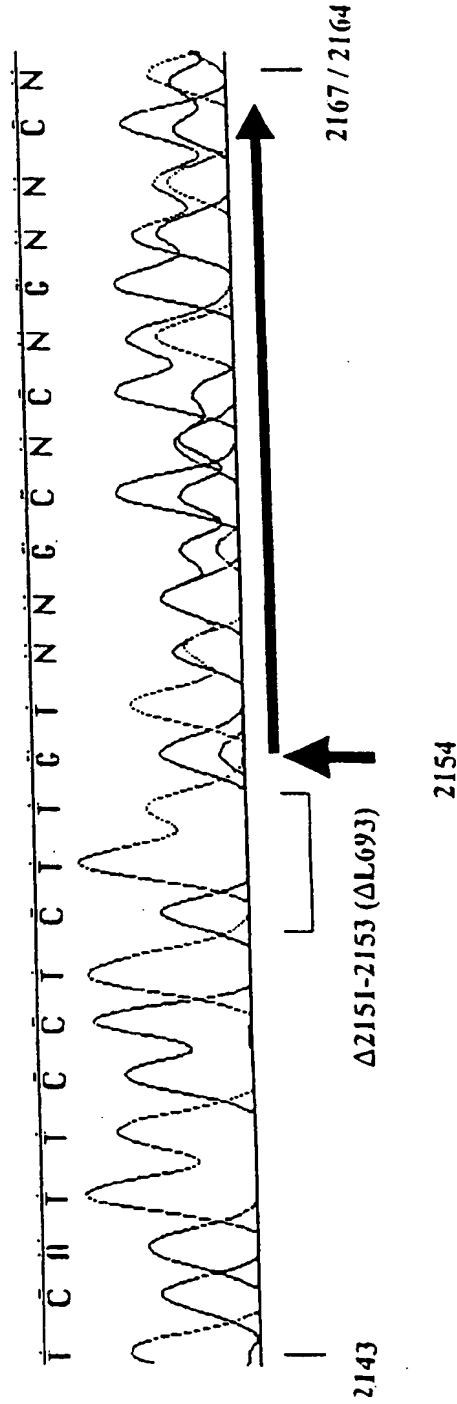


Fig. 6A

Exon 14
FHA-1

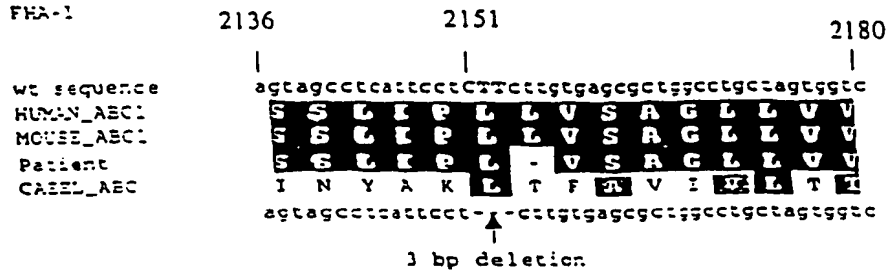


Fig. 6B

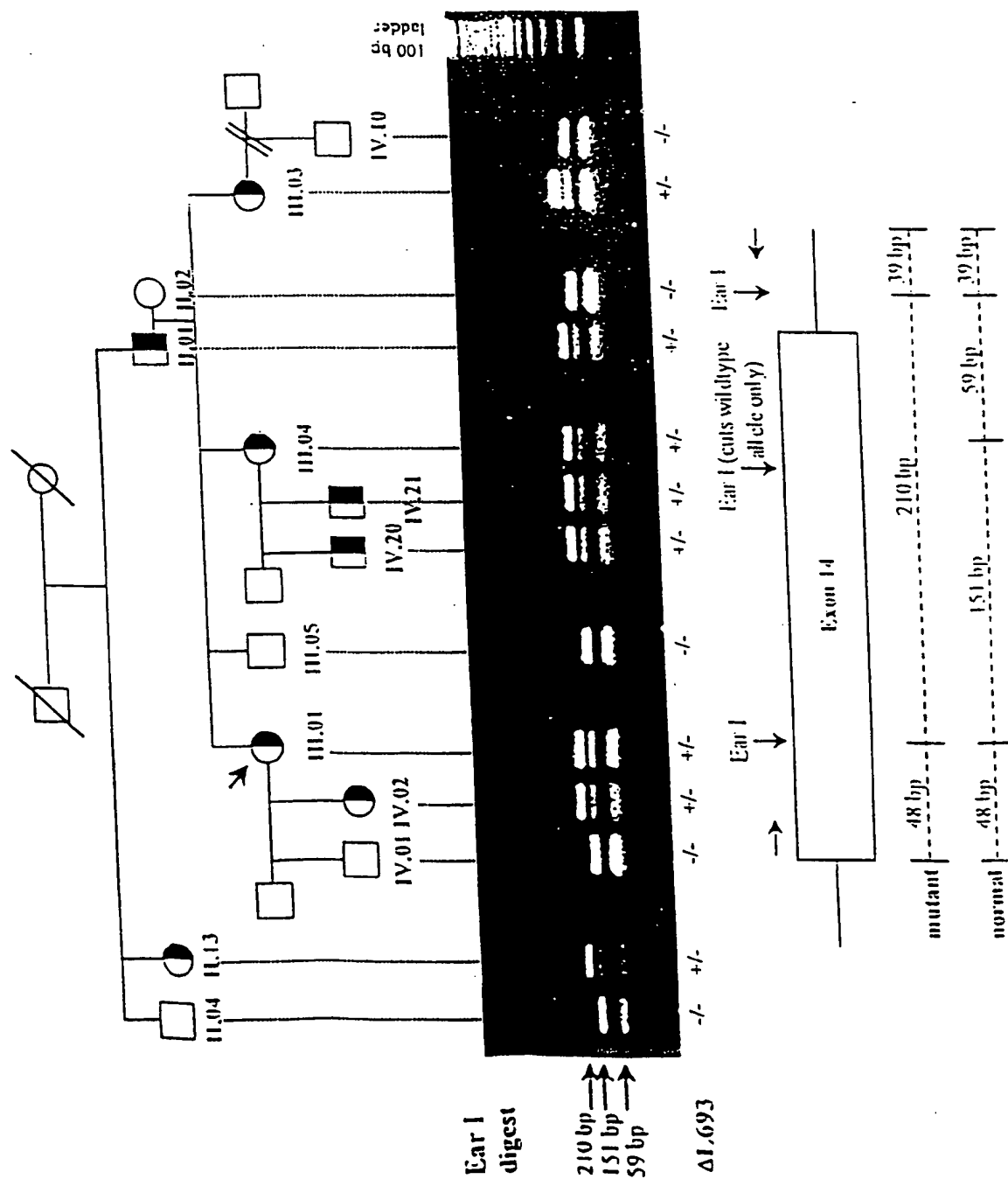


Fig. 6C

Exon 41

FHA-J

wt sequence

HUMAN_AEC1

MOUSE_AEC1

Patient (Δ E1893, D1894)

CASEL_AEC

 Δ 5752-5757

5740

5752

5775

aattgat					gaagat	GAA	CA	TG	CG	GG
S D - - -					E D E D V R R E R Q					
I D - - -					E D E D V R R E R Q					
I D - - -					E D - - V R R E R Q					
D E R D V					E D S D V I A E E S					
aattgat					gaagat	-----	gt	gag	g	g
							↑			
							6 bp deletion			

Fig. 6E

Exon 48 mutation:

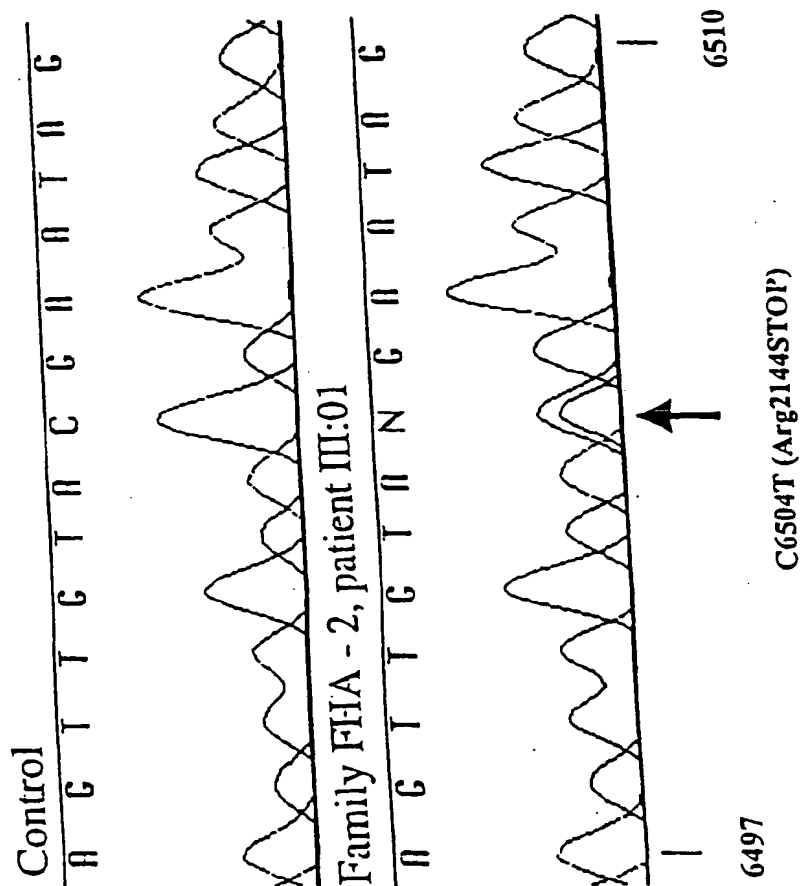


Fig. 6

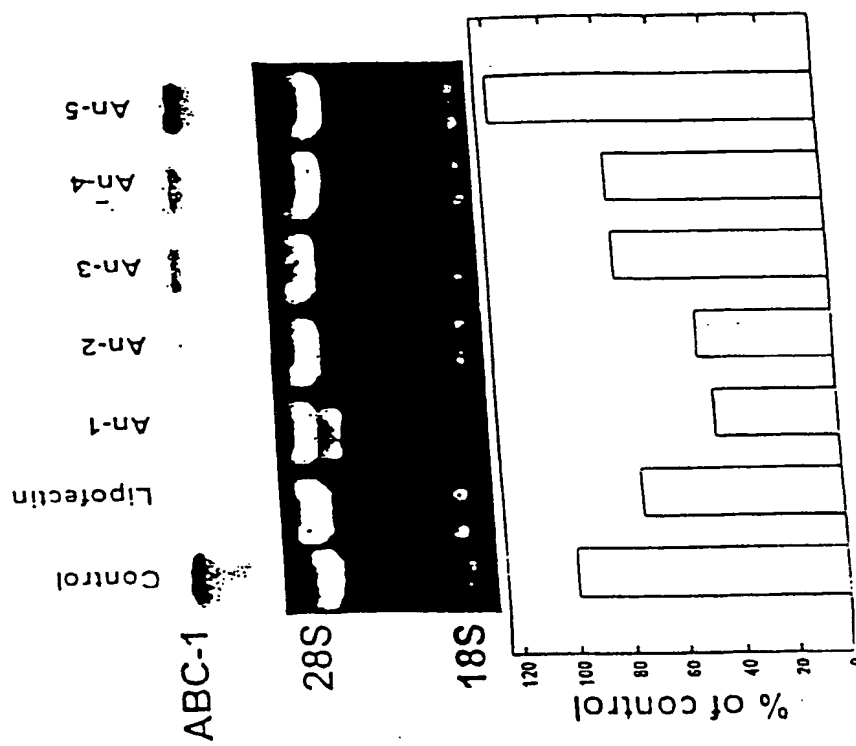


Fig. 7A

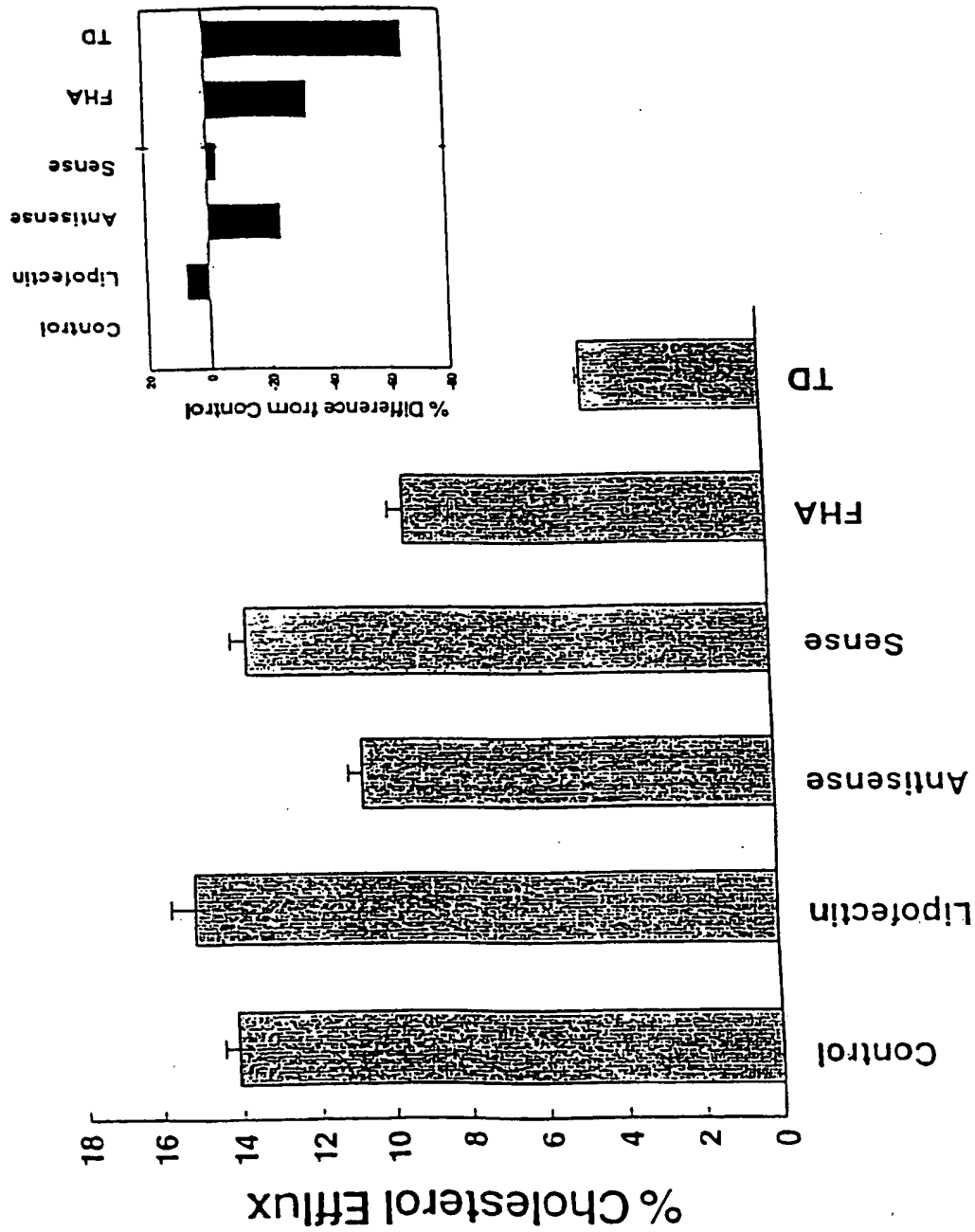


Fig. 7B

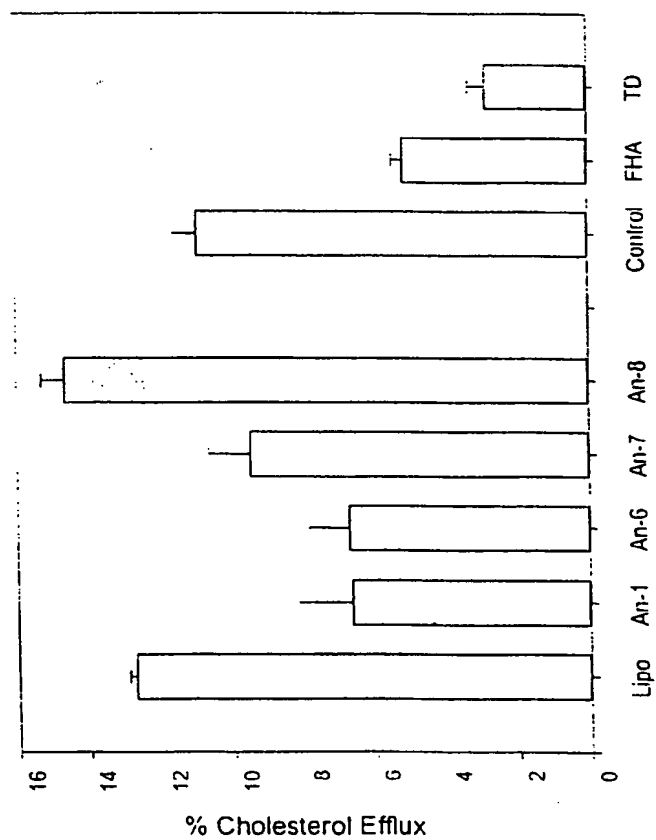
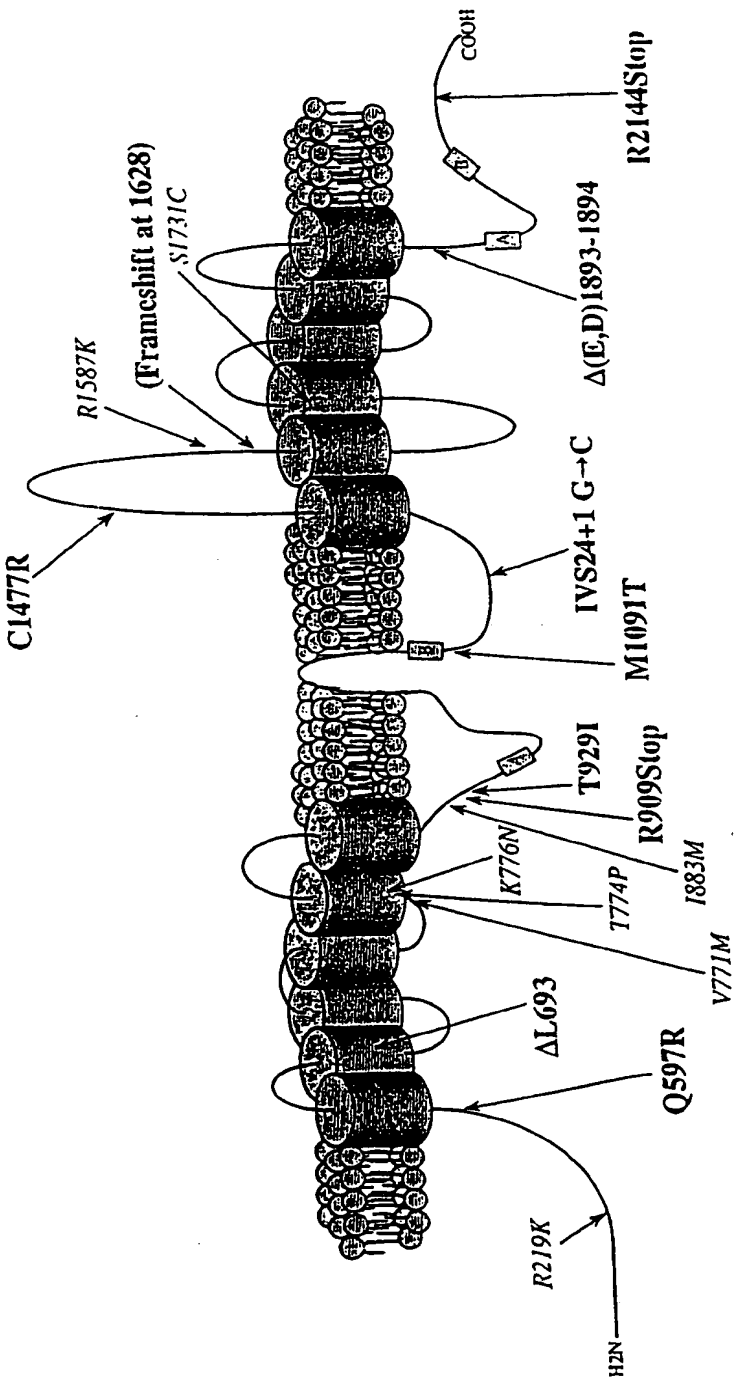


Fig. 7C

002



Mutation
Polymorphism

Fig. 8

SEQ ID NO: 1

MACWPQLRLLLWKNLTFRRRQTCQLLLEVAWPLFIFLILISVRLSYPPYEQHECHFPNKAMPSAGTLPWVO
GIICNANNPCFRYPTPGEAPGVVGNFNKSIVARLFSDAARRLLYSQKDTSMKDMRKTLRTLOQIKKSSSNL
KLQDFLDVNETFSGFLYHNLSLPKSTVDKMLRADVILHKVFLQGYQLHLTSLCNGSKSEEMIQLGDQEVSE
LCGLPREKLAARVLRNMDILKPIRLTLNSTSPFPSEKELAEATKTLHSLGTLAQLFSLMRWSWDMRQE
VMFLTNVNSSSSSTQIYQAVSRIVCGHPEGGLKIKSLNWEYEDNNYKALFGGNGTEEDAETFYDNSTTPYC
NDLMKNLESSPLSRIIWKALKPLLVGKILYTPDTPATRVMAEVNKTFOELAVFHDLEGMWEELSPKIWTF
MENSQEMDLVRMLLDSRDNDFWEQQLDGLDWTADIVAFKHPEDVQSSNGSVYKREAFNETNQAIRT
ISRFMECVNLNLEPIATEVWLINKSMELDERKFWAGIVFTGITPGSIELPHHVKYKIRMDIDNVERTNK
IKDGYWDPGPRADPFEDMRYVWGGFAYLQDVVEQAIIRVLTGTEKKTGVYMQMPYPCYVDDIFLRVMSRS
MPLFMTLAWIYSVAVIIKGIYVEKEARLKETMRIMGLDNSILWFSWFISSLIPLLVSAGLLVILKLGILL
PYSDPSVVFVFLSVFAVVTILQCFLISTLFSRANLAAACGGIIYFTLYLPYVLCVAWQDYVGFGLKIFASL
LSPVAFGFGCEYFALFEEQIGVQWDLNFESPEEDGFNLTTSSMMLFDTFLYGVMTWYIEAVFPGQYGI
PRPWYFPCTKSYWFGESDEKSHPGSNQKRISIEICMEEEPHTLKLGVSIQNLVKVYRDGMKVAVDGLALNF
YEGQITSFLGHNGAGKTTTMSILTGLFPPTSGTAYILGKDIRSEMSTIRQNLGVCPQHNVLFDMLTVEEHI
WFYARLKGLSEKHVKAEMEQMALDVGLPSSKLKSKTSQSSGGMQRKLSVALAFVGGSKVVILDEPTAGVDP
YSRRGIWELLKYRQGRITILSTHMDADVLGDRIAIISHGKLCCVGSFLKNQLGTGYLTLVKKQVE
SSLSSCRNSSSTVSYLKEDSVSQSSSDAGLGSDESHTLTIDVSAISNLIRKHVSEARLVEDIGHELTYV
LPYEAKEGAFVELFHEIDRLSDLGISSYGISETTLEEFLKVAEESGVDAETSDGTLPARNRRAFGDK
QSCLRPFTEDDAADPNDSIDPESRETDLLSGMDGKGSYQVKGWKLTOQQFVALLWKRLLIARRSRKGFFA
QIVLPVAVFVCIALVFLVPPFGKYPSELEQPMYNEQYTFVSNDAPEDTGTLELLNALTKDPGFGTRCME
GNPIPDTPCQAGEEETAPVPQTIMDLFQNGNWTMNPSPACQCSSDKIKKMLPVCPPGAGGLPPQORQ
NTADILQDLTGRNISDYLKTYVQIIAKSLKNKIWVNEFRYGGFSLGVSNTOALPPSQEVNDAIKQMKHKL
KLAKDSSADRFLNSLGRFMTGLDTRNNVKVWFNNKGWHAISSFLNVINNAILRANLOKGENPSHYGITAFN
HPLNLTKQQLSEVALMTTSDVLVLSICVIFAMSFVPASFVFLIQERVSKAKHLQFISGVKPIVYLSNFV
WDMCNYVVPATLVIIIFICFOQKSYVSSNTLPVLALLLLLYGWSITPLMPASFVFKIPSTAYVVLTSVNL
FIGINGSVATFVLELFTDNKLNINDILKSVFLIFPHFCLGRGLIDMVKNQAMADALERFGENRFVSPLSW
DLVGRNLFAMAVEGVVFFLITVLIQYRFFIRPRPVNAKLSPLNDEDEDVRRERQRIIDGGGQNDILEIKEL
TKIYRRKRKPAVDRI CVGIPPGEFCGLLGVNGAGKSSTFKMLTGDTTVTRGDAFLNKNLSILSNIHEVHQNM
GYCPOFDAITELLTGREHVEFFALLRGVPEKEVGKVGWEAIRKLGLVKYGEKYAGNYSGGNKRKLSTAMAL
IGGPPVFLDEPTTGMDPKARRFLWNCALSVVKEGRSVVLTSHSMEECEALCTRMAIMVNGRFRCLGSVQH
LKNRFGDGYTIVVRIAGSNPDLKPVDFFGLAFPGSVLKEKHRLMLQYQLPSSLSLARIFSILSQSKRL
HIEDYSVSQTTLDQVFNFAKQSDDDLKOLSLHKNQTVVDVAVLTSFLQDEKVKESYV*

Fig. 9A

SEQ ID NO: 2

GTCCCTGCTGTGAGCTCTGGCCGCTGCCTTCCAGGGCTCCCGAGCCACACGCTGGGGGTG
CTGGCTGAGGGAACATGGCTTGTGGCCTCAGCTGAGGTTGCTGCTGTGGAAGAACCCTCA
CTTTCAGAAGAAGACAAACATGTCAGCTGTTACTGGAAGTGGCCTGGCCTCTATTTATCT
TCCTGATCCTGATCTCTGTTGGCTGAGCTACCCACCCTATGAACAACATGAATGCCATT
TTCCAAATAAAGCCATGCCCTCTGCAGGAACACTTCCTTGGGTTGAGGGGATATCTGTA
ATGCCAACAAACCCCTGTTTCCGTTACCCGACTCCTGGGGAGGCTCCCGGAGTTGTTGGAA
ACTTTAACAAATCCATTGTGGCTCGCTGTTCTCAGATGCTCGGAGGCTCTTTTATACA
GCCAGAAAGACACCAGCATGAAGGACATGCGCAAAGTTCTGAGAACATTACAGCAGATCA
AGAAATCCAGCTCAAACTTGAAGCTTCAAGATTTCTGGTGGACAATGAAACCTTCTCTG
GGTTCCTGTATCACAACCTCTCTCTCCAAAGTCTACTGTGGACAAGATGCTGAGGGCTG
ATGTCATTCTCCACAAGGTATTTTGAAGGCTACCAGTTACATTTGACAAGTCTGTGCA
ATGGATCAAAATCAGAAAGAGATGATTCAACTTGGTGACCAAGAAGTTTCTGAGCTTTGTG
GCCTACCAAGGGAGAAACTGGCTGCAGCAGAGCGAGTACTTCGTTCCAACATGGACATCC
TGAAGCCAAATCCTGAGAACACTAAACTCTACATCTCCCTCCCGAGCAAGGAGCTGGCTG
AAGCCACAAAACATTCTGCATAGTCTTGGGACTCTGGCCAGGAGCTGTTGAGCATGA
GAAGCTGGAGTGACATGCGACAGGAGGTGATGTTTCTGACCAATGTGAACAGCTCCAGCT
CCTCCACCCAAATCTACCAGGCTGTGTCTCGTATTGTCTGCGGCATCCCGAGGGAGGGG
GGCTGAAGATCAAGTCTCTCAACTGGTATGAGGACAACAATAACAAGCCCTCTTTGGAG
GCAATGGCACTGAGGAAGATGCTGAAACCTTCTATGACAACCTTACAACCTCTTACTGCA
ATGATTTGATGAAGAAATTTGGAGTCTAGTCTCTTTCCCGCATTATCTGGAAGCTCTGA
AGCCGCTGCTCGTTGGGAAGATCCTGTATACACCTGACACTCCAGCCACAAGGCAGGTCA
TGGCTGAGGTGAACAAGACCTTCCAGGAACCTGGCTGTGTTCCATGATCTGGAAGGCATGT
GGGAGGAACCTCAGCCCAAGATCTGGACCTTCATGGAGAACAGCCAAGAAATGACCTTG
TCCGGATGCTGTTGGAACAGCAGGACAATGACCACTTTTGGGAACAGCAGTTGGATGGCT
TAGATTGGACAGCCCAAGACATCGTGGCCTTTTGGCCAAGCACCCAGAGGATGTCCAGT
CCAGTAATGTTCTGTGTACACCTGGAGAGAAGCTTTCAACGAGACTAACCAGGCAATCC
GGACCATATCTCGCTTCATGGAGTGTGTCAACCTGAACAAGCTAGAACCCTATAGCAACAG
AAGTCTGGCTCATCAACAAGTCCATGGAGCTGCTGGATGAGAGGAAGTTCTGGGCTGGTA
TTGTGTTCACTGGAAATTAATCCAGGCAGCATTGAGCTGCCCCATCATGTCAAGTACAAGA
TCCGAATGGACATTGACAAATGTGGAGAGGACAAATAAAATCAAGGATGGGTACTGGGACC
CTGGTCCTCGAGCTGACCCCTTTGAGGACATGCGGTACGTCTGGGGGGGCTTCGCCTACT
TGCAGGATCTGGTGGAGCAGGCAATCATCAGGGTGCTGACGGGCACCGAGAAGAAAATG

Fig. 9B

GTGTCATATGCAACAGATGCCCTATCCCTGTTACGTTGATGACATCTTTCTGCGGGTGA
TGAGCCGGTCAATGCCCCCTCTTCATGACGCTGGCCTGGATTTACTCAGTGGCTGTGATCA
TCAAGGGCATCGTGATGAGAAGGAGGCACGCTGAAAGAGACCATGCGGATCATGGGCC
TGGACAAACAGCATCCTCTGGTTTAGCTGGTTTCATTAGTAGCCTCATTCTCTCTTGTGA
GCGCTGGCCTGCTAGTGGTCATCCTGAAGTTAGGAAACCTGCTGCCCTACASTGATCCCA
GCGTGGTGTTTGTCTTCTGTCCTGTCCTGTTTGTCTGTGGTGACAACTCTGCAGTGCTTCTGA
TTAGCACACTCTTCTCCAGAGCCAACCTGGCAGCAGCCTGTGGGGGCATCATCTACTTCA
CGCTGTACCTGCCCTACGTCCTGTGTGTGGCATGGCAGGACTACGTGGGCTTCACACTCA
AGATCTTCGCTAGCCTGCTGTCTCTCTGTGGCTTTTGGGTTTGGCTGTGAGTACTTTGCCC
TTTTTGAGGAGCAGGGCATTGGAGTGCAGTGGGACAACCTGTTTGAGAGTCTGTGGAGG
AAGATGGCTTCAATCTCACCACCTTCGGTCTCCATGATGCTGTTTGACACCTTCTCTATG
GGGTGATGACCTGGTACATTGAGGCTGTCTTTCAGGCCAGTACGGAATTCCCAGGCCCT
GGTATTTTCTTGACCAAGTCTCTACTGGTTTGGCGAGGAAAGTGATGAGAAGAGCCACC
CTGGTTCCAACCAGAAGAGAAATATCAGAAATCTGCATGGAGGAGGAACCCACCCACTTGA
AGCTGGGCGTGTCCATTGAGAACCTGGTAAAGTCTACCGAGATGGGATGAAGGTGGCTG
TCGATGGCCTGGCACTGAATTTTATGAGGGCCAGATCACCTCCTTCTGGGCCACAATG
GAGCGGGGAAGACGACCACCATGTCAATCTGACCGGTTGTTCCCCCGACCTCGGGCA
CCGCCTACATCTGGGAAAAGACATTGCTCTGAGATGAGCACCATCCGGCAGAACCTGG
GGGTCTGTCCCCAGCATAACGTGCTGTTTGACATGCTGACTGTGGAAGAACACATCTGGT
TCTATGCCCGCTTGAAAGGCTCTCTGAGAAGCACGTGAAGGCGGAGATGGAGCAGATGG
CCCTGGATGTTGGTTTGCCA TCAAGCAAGCTGAAAAGCAAAACAAGCCAGCTGTGAGGTG
GAATGCAGAGAAAGCTATCTGTGGCCTTGGCCTTTGTGCGGGGATCTAAGGTTGTATTCT
TGGATGAACCCACAGCTGGTGTGGACCCCTTACTCCCGCAGGGGAATATGGGAGCTGCTGC
TGAAATACCGACAAGGCCGACCATTTCTCTCTACACACCACATGGATGAAGCGGACG
TCCTGGGGGACAGGATTGCCATCATCTCCATGGGAAGCTGTGCTGTGTGGGCTCCTCCC
TGTTTCTGAAGAACCAGCTGGGAACAGGCTACTACCTGACCTTGGTCAAGAAAAGATGTGG
AATCCTCCCTCAGTTCTCTGCAGAAACAGTAGTAGCACTGTGTATACCTGAAAAAGGAGG
ACAGTGTCTCTCAGAGCAGTTCTGATGCTGGCCTGGGCAGCGACCATGAGAGTGACACGC
TGACCATCGATGTCTCTGCTATCTCCACCTCATCAGGAAGCATGTGTCTGAAGCCCGGC
TGGTGAAGACATAGGGCATGAGCTGACCTATGTGCTGCCATATGAAGCTGCTAAGGAGG
GAGCCTTTGTGGAACTCTTTCATGAGATTGATGACCGGCTCTCAGACCTGGGCATTTCTA
GTTATGGCATCTCAGAGACGACCCTGGAAGAAATATTCCTCAAGGTGGCCGAAGAGAGTG
GGGTGGATGCTGAGACCTCAGATGGTACCTTGCCAGCAAGACGAACAGGCGGGCCTTCG
GGGACAAGCAGAGCTGTCTTCGCCCCTCACTGAAGATGATGCTGCTGATCAAATGATT

Fig. 9C

CTGACATAGACCCAGAATCCAGAGAGACAGACTTGCTCAGTGGGATGGATGSCAAAGGGT
CCTACCAGGTGAAAGGCTGGAAACTTACACAGCAACAGTTTGTGGCCCTTTTGTGGAAGA
GACTGCTAATTGCCAGACGGAGTCGGAAGGATTTTTTGCTCAGATTGCTTGGCAGCTG
TGTTTCTCTGCATTGCCCTTGTGTTAGCCTGATCGTGCCACCCTTTGGCAAATACCCCA
GCCTGSACTTCAGCCCTGGATGTACAACGAACAGTACACATTGTGCAAAATGATGCTC
CTGAGGACACGGGAACCCTGGAACCTTTAAACGCCCTCACCAAGACCCTGCTTTCGGGA
CCCGCTGTATGGAAGGAAACCAATCCAGACACGCCCTGCCAGGCAGGGGAGGAAGAGT
GGACCACTGCCCCAGTTCCCCAGACCATCATGGACCTCTCCAGAATGGGAACCTGGACAA
TGCAGAACCCCTTCACTGCATGCCAGTGTAGCAGCGACAAATCAAGAAGATGCTGCCTG
TGTGTCCCCCAGGGGAGGGGGGCTGCCTCCTCCACAAAGAAAACAAACACTGCAGATA
TCCTTCAGGACCTGACAGGAAGAAACATTTCCGATTATCTGGTGAAGACGTATGTGCAGA
TCATAGCCAAAAGCTTAAAGAACAAGATCTGGGTGAATGAGTTTAGGTATGGCGGCTTTT
CCCTGGGTGTAGTAATCTCAAGCACTTCTCCGAGTCAAGAAGTTAATGATGCCATCA
AACAAATGAAGAAACACCTAAAGCTGGCCAAGGACAGTTCTGCAGATCGATTCTCAACA
GCTTGGGAAGATTTATGACAGGACTGGACACCAGAAATAATGTCAAGGTGTGTTCAATA
ACAAGGGCTGGCATGCAATCAGCTCTTCTGAATGTATCAACAATGCCATTCTCCGGG
CCAACCTGCAAAAGGGAGAGAACCCTAGCCATTATGGAATTACTGCTTTCAATCATCCCC
TGAATCTCACCAAGCAGCAGCTCTCAGAGGTGGCTCTGATGACCACATCAGTGGATGTCC
TTGTGTCCATCTGTGTCTCTTTGCAATGTCTTCCGTCCAGCCAGCTTTGTCTGATTCC
TGATCCAGGAGCGGGTCAAGCAAAGCAAAACACCTGCAGTTCTCAGTGGAGTGAAGCCTG
TCATCTACTGGCTCTCTAATTTGTCTGGATATGTGCAATTACGTTGTCCCTGCCACAC
TGGTCATTATCATCTTCTATCTGCTTCCAGCAGAAGTCTATGTGTCTCCACCAATCTGC
CTGTGCTAGCCCTTCTACTTTTGTCTGTATGGGTGGTCAATCACACCTCTCATGTACCCAG
CCTCCTTTGTGTTCAAATATCCCCAGCACACCTATGTGGTGTCTACCAGCGTGAACCTCT
TCATTGGCATTAAATGGCAGCGTGGCCACCTTTGTGCTGGAGCTGTTACCGACAATAAGC
TGAATAATATCAATGATATCCTGAAGTCCGTGTTCTTGATCTTCCACATTTTTCCTGG
GACGAGGGCTCATCGACATGGTGAAAAACAGGCAATGGCTGATGCCCTGGAAGGTTTG
GGGAGAATCGCTTTGTGTACCATTTCTTGGGACTGGTGGGACGAAACCTCTTCGCCA
TGGCCGTGGAAGGGGTGGTGTCTTCTCTATTACTGTTCTGATCCAGTACAGATTCTTCA
TCAGGCCCAGACCTGTAAATGCAAAGCTATCTCCTCTGAATGATGAAGATGAAGATGTGA
GGCGGGAAGACAGAGAATTCTTGATGGTGGAGGCCAGAATGACATCTTAGAAATCAAGG
AGTTGACGAAGATATATAGAAGGAAGCGGAAGCCTGCTGTTGACAGGATTTGCGTGGGCA
TTCTCCTGTGTGAGTGTCTTGGGCTCTGGGAGTTAATGGGGCTGGAAAATCATCAACTT
TCAAGATGTTAACAGGAGATACCACTGTTACCAGAGGAGATGCTTCTTAAACAAAAATA

Fig. 9D

GTATCTTATCAAACATCCATGAAGTACATCAGAACATGGGCTACTGCCCTCA3TTTGATG
CCATCACAGAGCTGTTGACTGGGAGAGAACACGTGGAGTTCTTTGCCCTTTT3AGAGGAG
TCCCAGAGAAAGAAGTTGGCAAGGTTGGTGAGTGGGCGATTCCGAAACTGG3CTCGTGA
AGTATGGAGAAAAATATGCTGGTAACTATAGTGGAGGCAACAAACGCAAGCTCTCTACAG
CCATGG3CTTTGATCGGCGGGCCTCCTGTGGTGTCTTCTGGATGAACCCACCA3AGGCATGG
ATCCCAAAGCCCGCGGTTCTTGTGGAATTGTGCCCTAAGTGTGTCAAGGA3GGGAGAT
CAGTAGTGCTTACATCTCATAGTATGGAAGAATGTGAAGCTCTTTGCACTA33ATGGCAA
TCAT33TCAATGGAAGGTTCAAGTGCCTTGGCAGTGTCCAGCATCTAAAAA3TAGGTTTG
GAGATG3TTATACAATAGTTGTACGAATAGCAGGGTCCAACCCGGACCTGAAGCCTGTCC
AGGATTTCTTTGGACTTGCAATTTCTGGAAGTGTCTTAAAGAGAAACACC3GAACATGC
TACAAATACCAGCTTCCATCTTCATTATCTTCTCTGGCCAGGATATTCAAGCATCCTCTCCC
AGAGCAAAAAGCGACTCCACATAGAAGACTACTCTGTTTCTCAGACAACACTTGACCAAG
TATTTGTGAACCTTTGCCAAGGACCAAAGTGATGATGACCACTTAAAGACCTCTCATTAC
ACAAAAACCAGACAGTAGTGGACGTTGCAGTTCTCACATCTTTTCTACAGGATGAGAAAAG
TGAAAGAAAGCTATGTATGAAGAATCCTGTTTATACGGGGTGGCTGAAAGTAAAGAGGAA
CTAGACTTTCTTTGCACCATGTGAAGTGTGTGGAGAAAAGAGCCAGAAGTTGATGTGG
GAAGAAGTAAACTGGATACTGTACTGATACTATTCAATGCAATGCAATTCAATGCAATGA
AAACAAAATTCCATTACAGGGGCAGTGCCTTTGTAGCCTATGTCTTGATG3CTCTCAAG
TGAAAGACTTGAAATTTAGTTTTTTACCTATACCTATGTGAAACTCTATTATGGAACCCAA
TGGACATATGGGTTTGAACCTCACACTTTTTTTTTTTTTTTTGTTCCTGTGTATTCTCATT
GGGGTTGCAACAATAATTCATCAAGTAATCATGGCCAGCGATTATTGATCAAAATCAAAA
GGTAATGCACATCCTCATTCACTAAGCCATGCCATGCCAGGAGACTGGTTTCCCGGTGA
CACATCCATTGCTGGCAATGAGTGTGCCAGAGTTATTAGTGCCAAGTTTTTCAGAAAGTT
TGAAAGCACCATGGTGT3TCA7GCTCACTTTTGTGAAAGCTGCTCTGCTCAGAGTCTATCA
ACATTGAATATCAGTTGACAGAATGGTGCCATGCGTGGCTAACATCCTGCTTTGATTCCC
TCTGATAAGCTGTTCT33TGGCAGTAACATGCAACAAAAATGTGGGTGTCTCCAGGCACG
GGAAACTTGGTTCCATTGTTATATTGTCCATGCTTCGAGCCATGGGTCTACAGGGTCAT
CCTTATGAGACTCTTAAATATACTTAGATCCTGGTAAGAGGCAAGAATCAACAGCCAAA
CTGCTGGGGCTGCAACTGCTGAAGCCAG3GCATGGGATTAAGAGATTGTGCGTTCAAAC
CTAGGGAAGCCTGTGCCATTTGTCCCTGACTGTCTGCTAACATGGTACACTGCATCTCAA
GATGTTTATCTGACACAAGTGATTATTTCTGGCTTTTTGAATTAATCTAGAAAATGAAA

Fig. 9E

Exon	Exon Forward Primer	SEQ ID No.	Reverse Primer	SEQ ID No.	Intron (kb)	Intron (kb)
exon 1	140 GCTGATGATTAATGATGCTTCA	70	AATCCATCCTTCAATACACCA	119	intron 1	>6.413
exon 2	94 GGATTTCCAGATCCGACGTG	71	AGTCCATTTAGCCCACTT	120	intron 2	>4.21
exon 3	142 GACAGCTTGGCATGAGCA	72	CGAGCATCAAAATCTCC	121	intron 3	>1.248 (1.6)
exon 4	119 GCACTTGGCAGTCACTCTG	73	GGTGGCATCAATTTCCAT	122	intron 4	>1.512
exon 5	122 GTTCTTCCACTGTCCCAT	74	CCCTTCAGCCCATTTCCAT	123	intron 5	>1.589 (3)
exon 6	97 ACTTCAAGAGCCAGCTCC	75	TGTCAGAGAAAGGCTGAC	124	intron 6	>2.728 (10)
exon 7	93 TCGGTTCTTGTGTAAACTCA	76	AGGAGTCTTTCAGAGCTCA	125	intron 7	4.957
exon 8	241 TCCAGGCTTTGAGATGAC	77	AGGAGTCAACAGGCCAAG	126	intron 8	>2.311 (2.5)
exon 9	140 GGTCCAGGCCCTGTGA	78	CGCACCTCTGAAGCTACC	127	intron 9	0.332
exon 10	117 GCTGCTGTGATGGGTATCT	79	ACTCTACTCAACTTGGAA	128	intron 10	4.208
exon 11	196 TTGTAAATTTTGTAGTCTCTCA	80	GCCTGCTGCTGAGCTTAT	129	intron 11	0.747
exon 12	298 TAGTCAGCTCTTTCCTCTCA	81	CAAAATCATGACACCAAGTTAG	130	intron 12	0.523
exon 13	117 AAGGAGCTTGTAGGGGTA	82	CATGACATGGACACATA	131	intron 13	1.787
exon 14	223 GATGTGCTGCTCTCTAGC	83	CCATGACATGGACACATA	132	intron 14	1.747
exon 15	223 CAAGTGAATTTCTCCAGG	84	TGCTTTTATAGGGAGCTCA	133	intron 15	1.059
exon 16	203 GCAATTCATTTCTCCAGG	85	CCCTGCTGCTGAGAGATTC	134	intron 16	1.105
exon 17	114 TCAAGGAGGATGGACCTG	86	AGGCGAGGAGCATGCTT	135	intron 17	1.788
exon 18	172 CTGAAGTTCAAGCGCAGTG	87	GGGATCAGCATGTTTCTTA	136	intron 18	0.99
exon 19	132 TCCAGACTGATGGAGATC	88	GCTTAGTCCCACTGCTCC	137	intron 19	1.307
exon 20	143 GCGAGGAGACCTGTATCT	89	ATTTTCCTGCACTGTGT	138	intron 20	0.204
exon 21	138 AGGTCTCTGCTCTCACTCA	90	TCAAGAGCTTAGCATGA	139	intron 21	0.706
exon 22	221 CCAGTCTTACCCCTGCTAA	91	ACAGAGCGCTAGCATGA	140	intron 22	>0.865 (1.7)
exon 23	73 CACACACAGAGCTTCTTGA	92	TCAAGAGCGCTAGCATGA	141	intron 23	0.966
exon 24	203 ACCTGGACAGGTGTGTGT	93	ACTGGGCGCACATATATCA	142	intron 24	1.650
exon 25	49 GGGCTAACATGCCACTCAGTA	94	CTTCCCATCTGGCAACAC	143	intron 25	0.196
exon 26	114 GTTGTGCAATGGGGAAG	95	GCTAAGGGCATCTCAAGAA	144	intron 26	1.396
exon 27	149 CACCAAGAGGAGCATGG	96	TCAAGTGCATCTGGGCATA	145	intron 27	1.643
exon 28	125 CTGACCTGTAAGTAATTC	97	CTGAAGTGCATCTGGGCATA	146	intron 28	>0.728 (1.4)
exon 29	99 GCTGTACAGAGAAATGCTT	98	CAATGTGCTGCACTGTGT	147	intron 29	>2.589 (3)
exon 30	190 TTACGGAATGATCTGCTC	99	GAAGTACCAAGCCATCT	148	intron 30	1.521
exon 31	95 AGTCAAGTTCTGCTCAGAC	100	CATTTCGCCACTGTTTCA	149	intron 31	>0.944 (1)
exon 32	33 CCCTGCTTATCTCTCAGGTG	101	CAAGGCTTCTTCAATCA	150	intron 32	>1.062 (1.6.5)
exon 33	106 CTTTGTACACATCCCACTGA	102	CAAGGCTTCTTCAATCA	151	intron 33	1.475
exon 34	75 TGTGTCCAGGTTCCAGTA	103	CAAGGCTTCTTCAATCA	152	intron 34	0.522
exon 35	170 TGAGGTTTATGGGCTGTT	104	ATGCCCTGCGCAGTTTAC	153	intron 35	1.278
exon 36	178 ATGTTTCTTCTGCTGTC	105	CTCTGAGCTGTCCCTGAC	154	intron 36	>1.688 (2)
exon 37	116 ATCTGCTTCTTCTGCTGA	106	TATCATCATGCGCCCTGAC	155	intron 37	0.112
exon 38	145 AGGAGCTGCACAGTGGATA	107	AGAGTCCCTGCGCCCTGCT	156	intron 38	1.545
exon 39	124 TCACTCCCATATTCAAGCTTGA	108	AAGGAGCTCAGCAGTGTAA	157	intron 39	1.087
exon 40	121 GGTATGGAATTCGGTGA	109	CGATTCGATGAGTGTTCCT	158	intron 40	0.265
exon 41	83 AGTCTGCTTCCAGATTC	110	CCATTCGATGAGTGTTCCT	159	intron 41	>0.822 (0.9)
exon 42	107 GGTATGAGTGTATGGGCA	111	ATGCTGCATGTTTATGCTTC	160	intron 42	0.909
exon 43	142 CAGGAATATAGGCGGATTC	112	TCATGATGATTTTATGCTTC	161	intron 43	2.355
exon 44	135 CATGTATGTATGAGCAGCATGA	113	GGCTGTGGAAGCCATAG	162	intron 44	0.372
exon 45	104 CTGTTCAAGATGCTCTGTC	114	GGCTGTGGAAGCCATAG	163	intron 45	>1.059 (1.3)
exon 46	93 CTGAGGAGCTGGAATGCTG	115	TGCTGCATATCTAGTGGAAA	164	intron 46	0.483
exon 47	214 GGGTCCAGGATTCAGTAT	116	TGCTGCATATCTAGTGGAAA	165	intron 47	0.859
exon 48	214 GGGTCCAGGATTCAGTAT	117	GATCAGGAATTCAGGACAAA	166	intron 48	0.941
exon 49	295 CTTGACCTAATTCACATCTGG	118	TGCGTTCATATAGAGTTTCA	167		>1.075

Fig. 10

Polymorphisms in an ABC1 BAC contig					
Base/Intron	Nucleotide	Amino acid change		Sequence difference, position	SEQ ID NO:
5	G48A	no change	More common:	CTGGGTTCTGATATGACAA...	250
			Less common:	CTGGGTTCTATATGACAA...	251
5	G750A	R116K	More common:	AGCTATCAAGGAGGAGAA...	252
			Less common:	AGCTATCAAGGAGGAGAA...	253
Intron 7	G (+) 2363 T	Not applicable	Allele 1:	TTTAAAGGAGGATATACG...	254
			Allele 2:	TTTAAAGGAGGATATACG...	255
Intron 7	G (+) 3035 T	Not applicable	Allele 1:	CAAAATATTTTATTTT...	256
			Allele 2:	CAAAATATTTTATTTT...	257
8	C1610T	no change	More common:	CGGGGATCTCGAGGAGAG...	258
			Less common:	CGGGGATCTCGAGGAGAG...	259
8	G1622A	no change	More common:	AGGAGAGGAGGAGAGAG...	260
			Less common:	AGGAGAGGAGGAGAGAG...	261
Intron 8	(-) 42 ins. G	Not applicable	More common:	AGGAGAGGAGGAGGAG...	262
			Less common:	AGGAGAGGAGGAGGAG...	263
Intron 13	T (+) 24 A	Not applicable	More common:	AGGAGAGGAGGAGGAG...	264
			Less common:	AGGAGAGGAGGAGGAG...	265
15	A2584C	T774P	More common:	CGGAGAGGAGGAGGAG...	266
			Less common:	CGGAGAGGAGGAGGAG...	267
15	G2402C	K776H	More common:	CGGAGAGGAGGAGGAG...	268
			Less common:	CGGAGAGGAGGAGGAG...	269
Intron 14	C (+) 16 T	Not applicable	Allele 1:	CGGAGAGGAGGAGGAG...	270
			Allele 2:	CGGAGAGGAGGAGGAG...	271
17	A2773G	E883M	Allele 1:	AGGAGAGGAGGAGGAG...	272
			Allele 2:	AGGAGAGGAGGAGGAG...	273
Intron 17	C (-) 2000 G	Not applicable	Allele 1:	AGGAGAGGAGGAGGAG...	274
			Allele 2:	AGGAGAGGAGGAGGAG...	275
21	T3233G	no change	More common:	AGGAGAGGAGGAGGAG...	276
			Less common:	AGGAGAGGAGGAGGAG...	277
Intron 21	G (+) 118 T	Not applicable	Allele 1:	AGGAGAGGAGGAGGAG...	278
			Allele 2:	AGGAGAGGAGGAGGAG...	279
Intron 21	A (+) 863 C	Not applicable	Allele 1:	AGGAGAGGAGGAGGAG...	280
			Allele 2:	AGGAGAGGAGGAGGAG...	281
Intron 24	G (+) 321 T	Not applicable	Allele 1:	AGGAGAGGAGGAGGAG...	282
			Allele 2:	AGGAGAGGAGGAGGAG...	283
Intron 29	A (-) 824 G	Not applicable	Allele 1:	AGGAGAGGAGGAGGAG...	284
			Allele 2:	AGGAGAGGAGGAGGAG...	285
Intron 31	T (+) 20 C	Not applicable	More common:	AGGAGAGGAGGAGGAG...	286
			Less common:	AGGAGAGGAGGAGGAG...	287
Intron 33	A (+) 732 G	Not applicable	Allele 1:	AGGAGAGGAGGAGGAG...	288
			Allele 2:	AGGAGAGGAGGAGGAG...	289
Intron 33	C (+) 898 T	Not applicable	Allele 1:	AGGAGAGGAGGAGGAG...	290
			Allele 2:	AGGAGAGGAGGAGGAG...	291
Intron 34	C (+) 234 T	Not applicable	Allele 1:	AGGAGAGGAGGAGGAG...	292
			Allele 2:	AGGAGAGGAGGAGGAG...	293
34	G4834A	R1597K	More common:	AGGAGAGGAGGAGGAG...	294
			Less common:	AGGAGAGGAGGAGGAG...	295
37	C5266G	S1731C	More common:	AGGAGAGGAGGAGGAG...	296
			Less common:	AGGAGAGGAGGAGGAG...	297
Intron 43	T (+) 18 C	Not applicable	More common:	AGGAGAGGAGGAGGAG...	298
			Less common:	AGGAGAGGAGGAGGAG...	299
Intron 43	A (-) 1885 G	Not applicable	Allele 1:	AGGAGAGGAGGAGGAG...	300
			Allele 2:	AGGAGAGGAGGAGGAG...	301
48	C8521T	no change	More common:	AGGAGAGGAGGAGGAG...	302
			Less common:	AGGAGAGGAGGAGGAG...	303
Intron 10	(-) 14 ins. T	Not applicable	More common:	AGGAGAGGAGGAGGAG...	304
			Less common:	AGGAGAGGAGGAGGAG...	305
Exon 18	G2547A	V825M	More common:	AGGAGAGGAGGAGGAG...	306
			Less common:	AGGAGAGGAGGAGGAG...	307
Polymorphism in an ABC1 BAC contig:					
The polymorphism is within approximately 200 bp of the ABC1 gene					
A or G	Not applicable	Allele 1:	TTGGAGGCTGAGGAGGAG...	TTGGAGGCTGAGGAGGAG...	308
					309

Fig. 11

SEQ ID NO: 14

Genomic contig containing ABC1 exon 1:

underline = putitive promotor element

accccccttagaataatgataaattccctctggaatgattggataaactcatttcacccctgacttttaccctggaggagattt
cttaccctctttggctcttcaaatcttgactattaaaaatgttgcccttaaaaaatagggaacacagtttcaggggggaggtac
cagcccatgacccctctgcaaggcccccctaactcaaggttagttccctggaaactgtgggttatggaatgtttcaggaggt
gtgaggagctataatttaaggctgtccttagcaaggataccccctaaggatagaggggccagtagcattctggaggccagaa
aagttaaaactgaggcagtcagattagcttcagggtcaattaaagctgagggtcagccgggagaaattgcaggatgact
ctcaataccccctccccccccacagcagccacgatctgtctgtctttaatcatgggtgcagtgaaacctgtctcttcca
gggtgtcttgcccttcagtaacctgtgttaggcttgtccctgaacgtggctaccgataccaaagacatgatacagagaggc
aattagagaaacagacacttttccaaagcaagcatgtctgttgggcttagaagtttcatagtcctaataattataggacct
ctgcactctctggagatgaggcacatgagtcatactctgtgattctgtcttctgtgtcaacatctcatgaataggcaat
cagagctctggcaccaatgtattttcagttcatatctgatgtagttaaaatccacctctgtctgtagttttactggcaa
gggtgttttgataaagacatctagaacactgtaaaatatataacatttttatttgcctattataacctcaattacgaaaa
agacatctagaagcaacctcatcaagagagatactgaggccgggcatggtagctcacactgcaactgcaatccccattactttgg
gaggtctgaggcggtagatcacttgagggtcaagagtctgaaaacagacctggccaacatgttgaaacctctgtctctatta
aaaaatacaaaaaagttagctgggcttggtgggtgggcacctgtaatccagctactccggaggctgaggcaggagaataca
cttgaaacctgggaggcagaggttgacgtgagctgagatcacaccactgcactccaactcgggcaccagagtgagattac
atctaaaaaataaaaaataagtaataaaaaagagagataattgtagtctgttgggaaatttcaacttccatctcactctc
tggttaaccttttggagagttgttgaaacaaagtggaaatacacgcacatacacacacacataactctctgtttgtttaa
ggtttaagtgaatagctgtcatataactcagtttttgaaaggaggagaaattagttgctatttgtaattttgggtatgt
gcaactatttgatagaactctgagaaatgcattcagaacaacaaacataagtagagaataagctaagtgagggaagg
gcataataagagctgtgaaaaagcttattcttgagaaacaggactctaattgctaggcaagtcaactgtcttgggggaggc
ctcagctctctgtctataagattgcagcaggggtgtagtggaatgagctctcaacatccaagagattttatctact
aatagcagctgcaaatggagcatgactttgtggaagctctctctctccaccagaggggcgaattctctgtcccagt
gagatgtgacacttgtatgataccctgacttggagacttccccctctgggaacacctgccccctcaggcatgagggtga
gtgcactctcttgataggagccagcactaaaagctcatgtgttggcagtgctcttgcgggaagggaagaccagccag
cccatttcttactgcacaagcaaacagctctctgtgtctgtacagatacatgcacttctctctctcactgtgttccat
agacagcttttagtgcgtgtagaagtagtaggggcagtcacgggaaggagttctgttttcttcttggctatgccaattg
ggaaaaatctctctatcttctgttttttagtgcatactctctctctctctctcttcttcttcttataattctcatctctcatc
tctctctgaaatgtgcatgtcaagttcaaaaagggcacaattgttttggtgagggaagggtgggagaacacgtgccaggtg
ctaaactagggtcatcattccccctctcacagccagctctctgtgaatgtgtgtgtgtgtgtgtgtgtgtgtgtgtgt
ctgtgtgtgtgtgtatttttttgcagcatcactgaattctgtctgtctgtgtgtgtttttaggttttgggttagggaaa
agttaaaagtaattttataatccagctgtcatttaagccaccttctgtgggtagcatattggtccactctccagttca
ttgtcttaagatgtcttcatcagaaaaggaataaactccaccccgctactctctgtcccccttactctgtttattttct
tctgtcaactcttaccaccaccacactgtgttgaaacaccactattttgtctgttccccactccctggtagaataagga
gccccatgaatgaggaaaccttgcctctgtgtctcaccactgaattcttaaggatggaacacacctggcatgtgatg
gcactcgataaaatattgttctggctcatgggacacttgacagagtttaaggctgcagttgttttgggaaattataagtg
taatgaatatttatctactattctcttccaaggcgatcacacaataatcaggctttacactccagttcttaggtct
tccaaagtatgactgtgagcttatccaaagctatgataatgagaaggcagtttatttgggtcagatttatttgatgtgta
ttaccacagtaagactcccccttcaaaaagctatgatgagtttgacaaatggatacacatgtgtatctaccactgcc
tgctctttcagctctgtctctccccccacccatgacacctgggtcacactgcagtgatttctgtccccctcatttcc
ctttctcagaatgtcatataaaatggaatcatcagatgtagtttttgtgtctgtcttattttctcttagcataggct
tttgggactctatccagggtgtgcgatacaagtagcttattctctttatggctgagtaagtgcccagttttatttta
tatatttatttatgaggaggttctcactctgtcaccagsgtggagtcggtagcgcgactcagctcactccaaact
ccgctctccagggtcaagcaattctctctgctctctgagtagctgggattacaggccaccacggccaccccaactaat
tttatacttttagtagagatcggtttcaccatgttggccagcgtgatctcaaaacttgacctcaggtgatccgcca
ctctctgctccccaaagtgctagattacaggcatgagccactgtgccagccccagttttatttattccaccagttgag
gtcttttcgacaactaatttcttccagtttttggtattctgtataaggctctataaaattatacacaataactagga
ggatgactgggtcatataatgactgtataaccttagcagaacactgtcaaaactatttccaaagtggtcttccatt
ttacaattccacagtgataatgactccaggtctccatcacactcagctagcatttataatttaatttagtgggtatgt
aatgatattccattgtgggttttaatttgcatctctctgcagctaatgatgagtggtttctgtcttatttgggaagggtttta
atttagcagctctgtgtatctgtagatatataaactcaaaatcatcagtggaattgcagttaaaaattctctaaaa
aattggccaaaggtttccagcagtcacttccatgcccaactgtatgaacaaggctgaggtgggaggtatgtcac
atctggcaaggagtagtaccacttgggtgactgatgagaccagagagctacgcctcgggcttgagggtgaggacggg
cgggaagtcagatgcagccctgtctggcttgggagggtgccagtccttagctaaagctggcagttatgggaaacag

Fig. 12
Page 1 of 30

aatagattctattacgttttccaggatgtccccaggagtcacctgggaagctcagcagctctttgtgactttcaagca
 atggtagaagctgtgaaacacagagctccctcttgggagataattggccaaatcaatcaatcaggcttgagaaatgag
 taccacaggtccaggagtgctgcccaccttgaaatttgacacacctatttctctatccgtctcttaattcaatcaagca
 facatccccaaagtgttacgacaagccagacccttttgcatactaaagaaaacagggatgaaagaaaacagaaaatgggtc
 ttgtctctgactcagaaggttagaaatctcttctccagccaagctctttagggagcagctaggaagggtctcgaaccc
 acgtgtcagcttcaggggaggatatacagaaaggacattgaagaagtggagacctaaagttagagacctaggcattagcc
 aggttagcagtgcttgaaaaagtgtcttaggacaagagaactcaccagtgaaagctccagtggttagggagagctggcagca
 tttctgagcctgtatacacatctccagggcatcttagcaggtccggagtgccagagagtagggtccagtcacaga
 agggaggccaggttagaccttgggtgagcactggactctatgtctcagctgctgaggagctggcaaaagggttttaagtcggg
 gagaggcatcttcagatatttgggttagctgagtaacttgggtgctctgtgacaaatgggttgggagaccagtgagggt
 gacgttgcgtcagcttaggagcaggatcagagtgccctattgactggatgactgtgaagtgggtgggtctccagccag
 taactggaaaatctgtatgagggcagaaagtgagtgactgcatctgaaacattgagaaatctagtacatagtactgtctc
 tttatattctttttttttttttttttttttgattttgggtttgtttgttctactaacttggaaaactgatgtggaatgtccct
 tggcttcagctacctcagcagaaggggcgggcatggccaaactctctcttaggacagaattgtctccagctattgat
 catctgtctctcagtgagggtgataatttctatatctgggtttgggtctgggtacggcaacactaggctattaaagttaactta
 ctgctttggccctctctatcttccagaaacccacaatggatttgctagaaataatggaaagctctgtttggacaggata
 taaccaatttctcagctagaggtattgttggatgaagaaagataaaatggggagaaagggaactcacattgctttggcac
 ttaaatgaagcattgtatgtgttgggaaatttatattatctctgtgaatccacagtagaacaacacagttgaacacca
 tacaaggttaagtattgtcatctcttatttaccatgaggaaatgtatgcttagagagcataaagccttggcaggggcac
 atagttgggaagccggggctaatctacgctgggtctcttctgtatagtttctcttttaattgtccctctctcattgt
 taccttggggatttcaagagattcatgtagcttctaaatcaacgaactgattctctggagagcagcttctgtatgagaaa
 aatctagctaatattttatttctagtgctctctggaatgcaagctctctctgagccacttagaaaacaatttgggatgac
 aagcatctgtctcaaatgtctctgtgtggttgccagtgctgtgctgagctgtcatcttgaacaaactgatgcagtgct
 tggcttaactctctctcttttggagtaagaaacttggaggcctctgtctcttagaagttgtctgagcaaatggtaa
 ggaaaagaaataggctctaaagccttgactatttccagaaatctcttgatttattggactgtcaatgaatgaattggaat
 acatagtggttaggtgtctcttctctcagacacttgcaatttctccaatctcttgactttcttagaagtttataatcca
 agtctctgttgggtgggtagataaaagggtattgttctactagagactgaccttggcatggagatctcatttggactcac
 agatttctagcttagcgttgggtttgtatccatccctcgtactgcatctctagttctcttctgtctcttgttctctcat
 gcccagcttcccacccctacccttgcctctactctcttagagggccacagtgatttctctgagccatttccataagcagat
 agggaggttcatggctaccaagtgccagcagggccgaatttccacctgtgtgctctctctctccattttctcatctctgc
 cccctcccagctttaaacttataataactacttgggactattccagcatataaataagggttaactgctggatgggtggc
 tgggatacacagaaatgtagatctcttgttccagagaagaccttctgcccctagcatggcaaacagctctccaaggagg
 cactctgacacccaacagagtaggggggggtgtgttccagtgccagtggaacaaagccagaaagtggtgcatatgtgct
 gacctgggagcttgtttgtcgttttccagcttgatgcccctgagcctgccaagcagacttgtttctccatgggatgtct
 gttttcttccagagacacagcgttaggggtgtctctcattacctgagagccaggtgtcggttagcattttcttgggtgttt
 actcacactcatctaaaggcagctgtgtgttttccagattaggaactgctttattgaggtgtcttttttttttttttt
 tgagacagagctctcgctctgtcgtccatgtcggagtgtagtgccacaacttgggtcactgcaectccgctccaggt
 cagcgattctcctgctcagcctcccagtagctgggactacaggtgcttgccacctgcccagctaaatttttgtatatt
 ttagtagagacgggggtttcacctgtattggctaggatgggtctcgatttcttgacctggtgactccgctccctcggcctcc
 caaagtctgggattataggcttgagccaccacgcttggcagatgggtgtttttatcatctgaaggactcagctgtatga
 accactgaaaatttagtatctaaaggaagttcagcgaatagctataagtcactccagccttgaggcaaaatttacaaatgc
 tectgacttctgtatgtaaggggagggcattttcttagaaaagagagcttaggtctctgggattccagtagccatttccat
 cctcagtggttttggccacctcagagaggtctatttccagaaatgcattctctattcccagatgataacatctatagaa
 ctaaaatgatttaggacctataacagctagcttagcctgtgtcggaaacacctcccgagctccctcttgggggtgaacc
 cagagccttgggagctggtgactcatgactccatgagaagcagtcagatgacagagctgtgtgttggaggtctcagctga
 gagggtggatttagcagctctcattgggtgtatgggttggcagcaataactgatgggtgttccccctctgtcttctct
 tcagttaatgaccagccacggcgtccctgtgtgagctctggccgctgcttccagggtccccagccacacgctgggg
 GTGCTGGCTGAGGGAAACATGGCTTGTGGCTCAGCTGAGGTTGCTGCTGTGGAAGAACCCTCACTTTCAGAAAGAAGACA
 AACAGtaagcttgggttttttagcagcgggggttctctcatttttcttcttgggttttgagttggggattggaggagg
 gaggggagggaaggaagctgttgggttttccacacagggaatgatggaatctggctcttatggacacagaactgtgtggt
 ccggatattggcatgtggcttatcatagagggcagatttgcagccaggtagaaaatagtagctttgggtctgtgctactgccc
 caggcataggttctgatctcaggacctggcctccgaatcgccccctgagcaccctcacttttctcttctgtgcagccctg
 ggaccacctggctctccaaaagccctctaatgggccccctgtatttctggaaagctgtgggtgaagtgagcttagtgcccca
 ctcttagagatcaatactgggtatcttgggtgtcaatctggattcttctctcaggcctggagggaatataataactgaga

Fig. 12
Page 2 of 30

cttggttttattctctgcagagggtctcaagccattcacttcccagatgggccaataatgcttctgagtaatctggagatca
cttttaatgcccaggtgaatggaaacctctccacagagggtatgtgagggctgtagagcagagtgaactccctgaaactca
gagtcagctctctgtctctctatctctgaacacctctcttagagatcccatctctaggatgcatctctctgtagtta
gtttctaagtcctctgtctctgtctctgctttatcttttttctctggattctaagccagtatccccacttggctgtctt
aatgtagcttaacatgtctgtaatcaaatgatcatcttctgagat:caaagggctataagggacttggagagaatt
tcattcagtttccctcaaaactagaataatgcttgcactgtctgtaaaagaacaaaagtgtcaaagcatccttttgttca
ctaaatttccctttttattatagtgttacttaaatattaggaagttaaaagtagggtataaacttcttataggctgttat
tatacaactatatgaccatacatatttacaaaattaagtgagccaaaattgcaaaatcaataccattcaaatataac
cttaaatgtgctgagggcagctgttctcaactgaaaccaaattataagttgcatggcagtaaatgctatcatgctgac
atcttgagtttggccagctctatatcatgtgctaatgattgaatttccaccccat:tttctacttgtatgaccttaa
cttgagcttggcaccctgttccatcctcatgagtttgctacaattatactgctgccaacacaatcataaacacaaatataaac
ctgggcttggaaatcttgtgcccagaacttggctttaaagtaagcat:taaaaaatccatatgtgtttatttagactttgt
ctagatgactgttgaatgaaaacaaagtgtttaaactcctcttagagaaacttaaatataatccctcagcaaatatgtat
acagatcttctcttgagaaaaactgattgtgttcagcctctcatgttacaaatggggaacctgaattctgaggtctcta
gtgagagaacagggactggaaatctgtggatcctatctgttttaataataattgtaaagtataatagataatattatatt
aaaaagagagrnnnnnnacacttagaatgagcttccatgtgtgaggcactaactgattaggcatatttaactagatttat
tcttttaaggccccgcgatgtactgttatttccacatgttgtagc:ggggaacgtgctactcagagaggttaagtaac
ctgtctgaggtccacaccactaacaaggagcacaggtagggttcaaa:ccagataa:ctgacttggagctggcactct
aactcaatgtgcctaatactgcttttcagtggtgtcattattttgcttctctccatc:gagaatattgaagtttctgact
ccttcttgcctttctccctgcttcccggtgttatccccaggtcttgggttccag:ccctctatgtccgctcttactct
tattcttctgtctacagtgtgatccagggctcctgccccttcttatcc:ggtagagggggccacttgcctgggaaattgtc
ccgccaatggtttatccatgttctgtgtccattagtgagtagtggaagaatcataatcatgttggcaatgaaagggggg
ctatggtctctgggtagtcttagtctgaactcttatttt

SEQ ID NO: 15

Genomic contig containing ABC1 exon 2:

[illegible]

Fig. 12
Page 4 of 30

ccaggcaattaacgtgggctaaattggacttttccaaagatgctgtctttgggaaacatcacacatgctttggatcagaa
aacctaggcttctaatttcttgataaggcatgaactcaggagactgttttcagtccctagtgaatgggtgataattgtaatt
ataacagtagacaacatctcttttacacattttaaatcatgaaaatagaataaccttactgataattttagaaagtgggtg
attaaaagcacatttaagataatgaccttaacacctagtctttccatgatgatgtcttaatacacacattgcaaatca
tggaacacagaatttt

Genomic contig containing ABC1 exon 3:

Page 6 of 30

tgtcttctctgcatcaggtcacctctctcacctctgtcactgccccatcagactacaatgtctgcagggtcttctccccct
gagtgtgagctccctgagcaaagcaggatgctgccccctcccccttgtattccttgctccttgcttcagtgcctgtacata
agtatgggcataataagtgtcccccaaatgagacattgaggattcttcaaatgcacaggaccgtgatgtgagttaggacg
cagtaaggacgatgggatgtggctcatgacaatcctgaggaagctgcagctgcggcacgcagggccacactgtcatgttc
atggaccctagactggcttctgtagcctccatgggcccccttccatacac

SEQ ID NO: 17

Genomic contig containing ABC1 exon 4:

ccatgactgccattggtataaagatgaatataatccagaccagattcatgattattcatacatttttagtgtattaaactt
caattctgcttttaaaataaaattaaaacatttctaataatgcccttaagagtatcccagcccaggccactgagcctactgt
ggttcattggataagtttgccctgggggcatgtgtgtgcatgcatgtgtgtgcacatgcatgatgagccgggcttgaag
ggtgtaagatttgggtgtgttagaccaatggagaaaaggcatttggggcagtgtatgatgggtgggggaggggaacatggtga
aatggagctgggtgtgggggagccatgggagtgggttagggccagcctgtggaggacctgggagccaggctgagttcta
gcacttggcagtcacttctgtaaagcagcagagcagcttggcctagctaaagccttctgccttttcttgaccctttac
agTGTGGCTCGCCTGTTCTCAGATGCTCGGAGGCTTCTTTTATACAGCCAGAAAGACACCAGCATGAAGGACATGCGCAA
AGTTCTGAGAAATTACAGCAGATCAAGAAATCCAGCTCAAgtaagttaaaaccttctctgcatccggtttataattggaa
attgacctgcaccagggaaagagagtagccagggtgtctggggcttgttcccattagatcttcccaagggttttctctc
cttgggtggctggcctgtggggccctctccaggaggcatgtgtgaagaaactaggggagctgggttgcacagacagtgtat
tactaatcttctctgggaagacagaagaaaagtccccaggggaagaatactacagacttggccttagggacagctagggg
gcagattgctgccaaactgcatttttctgaagttggccatatgggtgcagtgaaatggatttatagacagagtatttctg
gcataaagagcaattacagcttctaagttgatatggataagtgaaagtttaagcacttcttctaaaaagagaatgcaat
cattttccctaatcatttcaattagctctgatgggcatttgaacttgttctttaaagtgaaatctttacctctga
ctggtaagtatccaggcaatttcttgtgtgccaccaggaggtatctggggagtgaggcatttctgactgaggcattgg
ctgccatagcatcagagcagccttccaggcagtgccctggcaaggggacagaggctggtgggagcagctggctgagtga
gccagtaattggcatgt

SEQ ID NO: 18

Genomic contig containing ABC1 exon 5:

agcctctccagctgattctgactgcatacttaagtctggaaccattgcctgtgtttgcattaaacaggagattagctctctgc
agcctgtgggaataaaagctttaaactctctccaattttagcctctgtgcaaaaggcagctggggagacagggaatgaacgggacta
ctgcccaaaaagctcaggctgggggtgggtgagatcatctagaagagaaaagcaccggcctagggtgctcacgcctgtactgtca
ctactctggcagcgcaaggctggatcacaaagctcaggagattcgagaccagcttgcctatcatggtgaaacctgtct
ctactaaaga:aaaaaaaaaaaaaaatttggccagctcatggctgatcactctgaatcccagctactcgggagsgctgagg
aggagaatctcttgaaaccgggagcgggggtgacgtgagctgaga:ttccaccatcgactccaacctaggtgacagggt
tgagactccgctccaaaaataaaaaaaagaaaaggaaaaggctctgtgtgtgtgtatgtgtgtgtgtgtgtgtgtgtgt
ctgtgtgtgaacgacccatcacactgtgtgagtggaggacacatctcgagtgtggtctcaacatgttaccagaagcaat
atttcatgccctcctgtatctggcgatgtgctctctctatctcatctctgtgtgtgttagccagcaactgtgtgatcatca
atattatgataaacgtttctccactgtcccatgtgtcccaacttttttttttttttttgagttacttactaaataaaaaataaa
acactattcttcaatagACTTGAAGCTTCAAGATTTCCTGGTGGACATGAAAACCCTCTCTGGGTTCCTGTATCACAACC
TCTCTCTCCCAAAGTCTACTGTGGACAAGATGCTGAGGCTGTAGTCTATTCTCCAAAGgttaagctgtagctccagctt
ctccagttagggctgtatggcaattcagctgtgtgcagctactggaaagaaatgaataaaccttgtctcttgtaattggtgggtga
aggggagggcaggtagtttgaatacaacttcacttaatttttacttccctattcaggcaggaattgccaaacctccaggag
tggaatatcgcaacctggcgctcatggggccagctggttaaaataaaattgatctctggtcttactcctggcatttgtgatga
ttctctctcaaaagggaatcatcttaagtgtgagttaaactaaaaaaattcacagttctgaggcaataacctggtggttaa
gggttatgtctggaggagctctctctaaaaaaattgaggacaggagactctagacaagggtgtattgggaacttttaa
gaattttataaaaaaagggtcgagcgagtggcactgagctgagaactgtgtcttgccttgcattaaataggagatcagt
ccctgcagcttgttgggaataaggctttaaactctctcaattttagctctgtgagatggcactggggaaacagaaaatgaac
ggactagctgtcacaaagctcaggtgggatggccagatcattccaaaggtctgttaatcccagctcatatacccagcact
ctgggaagcgcaaggcggggaaaaactccttgagggtcaggagctcgagaccatctggcccaacaatgcaaaagcctgtctctac
taaaaaatatgaaaattagctcagcgtggtggcatgctcctgtagctccagctactcgtgaggtcgagacaggagaaatcgt
tgaaactctgggagcgggaggttcagtgagaccaatatacagccatcgactccagctggctgacagagtgagactccat
ctcaaaaaaaataaaaaaaagaaatttataaaaacaggaaataatattagtgtttatgttgaaattttaaacttgaat
catagaaaaacttctctggcatcatatttagacagctctgtgcagctgggtagcaccagacccagcttgcatgggttatg
attttttagagacactttttgagcttatctctctggcagaaaggggaaactgcttctctccctatctcgtgtctgcatacta
gcttgtctcttacaagaagcagaagtagtggaattgtttattcttgaaaaataagctttttgtcttcacatgatctagaattt
ttaaatttcaaaaaaatgtgcttactgcg

SEQ ID NO: 19

Genomic contig containing ABC1 exon 6:

agtaaaatggagaattccaaattctgaaattgtagaacatagttctgtgtctttagttaaataatcgacacttacagataa
atagcataaaatgctttctcccatatttcagcccagtcctacttaagacaacataaattgcaaaatagtgaggatgttg
tcatctataaaaagtgttccaggaattcagactctggattcctgtttgccaaatcatgtgtccactcttaagaaaac
gagttggactntggatTTTTCTTgcaagagggacaagagtggtggagatactgagcttaatgcaacttgcaggttttaag
tgctctgtcattgtgccttgtgctttgatacattctgagcttcagtaaagagacctgatgcattggactgttgcaatgga
acctgttttaagatcttcaagctgtattgatatgaagttctccaaaagacttcaaggaccagcttccaatcttcataa
tctctctgtgcttgtctctcttgcataaagtcttcagGTATTTTGCAAGGCTACCAGTTACATTGACAAAGTCTGT
GCAATGGATCAAAATCAGAAGAGATGATTCAACTTGGTGACCAAGAAGTTTCTGAGCTTTGTGGCCTACCAAGGGAGAAA
CTGGCTGCAGCAGAGCGAGTACTTCGTTCCAACATGGACATCCTGAAGCCAATCCTGgtgagtagacttgctcactggag
aaacttcaagcactaatgctttcggaaatgtgaggcttttcttggacagcatgactttgtttttagaaaaagtacggctg
gctgggagtttgtgatataatttagttcagtggtattctaagtgtctttagtggtcttccagacttttgggccatctccc
aaaggggtgaatgggaagaataagctgggtgtggctgagtttaagccaaaagtttttgtgcttgtttcaatcagagaaga
cctgctttttcatgtttttactattataataactaagcaagagctcatttgaaaacagagttcttcatatttaaaaaaaa
aagctctgaaaccattgatgggaagatggatatctatttatgtttaaaaacccatcataaagatgacattgtgggctgtc
acagttggaaggccctggaattagatgagaccacactatttagcttacttagtaataacattg

SEQ ID NO: 20

Genomic exon containing ABC1 exon 7 and 8:

ccgtttggcaaatgctcagtaaaagaaaagggttagaaggggagaaaaggcattttatcccaagccttcaggaatcaggat
gaggatgtcttcaccttggtggtggggagtaattatatacaattagagacagcacattggagtggtggctgatagctgtgtga
gatagctcttagctctctgcttagcagaggaaggacatttcaatagaagaaaaagttaaagacctgcccagaaacagag
aaaggatgtttgtcttttaagaagttagaaaaccctgtttgcagacaaaagccctccagttttggcagtaaaactttcatg
aaagggaaagaaaaggcaggggatgacattgttgacaattgtgaggaattaccatgtgccaggcactgtgaggggggtt
gtacatactctctagctcttagtgcttataaaaactctgtgatattgtgcacagcattttaaaactttgctgcatagtcgag
aaaatggaaggatgggggaatttgagtcatttggccagggttctatagctacccaggttcccatgactggagaattgggg
cacagggtgggggggagagtgagtgacaagaatcttaacacattcttattccattgagtccttaaaagaaagggtta
actaccacgttttttaagtttttcttaaatttaggttatgtggatctggcggttcttgttttgcctgggttgttttgtt
tttgcctatgctgtcttgaaacatctgtcatcttgtaggcctaaaggttaaacacaaaaacactttacctcctatagctttca
attaaagatctctcagtttgtgtttgtaatatgtttccaggcaagttctcccttaggttcgggttcttagtgtgttaacctt
agttataaagtgaacccaaagagagaaaagttagaaaacacacacactcactgttttgcctcatgaattactctcatggaa
ggaaacaattcatgaacacctctgcgtatcacagaggcctatctgagtcgtacgttttaagggagaccggttaggtccctttg
aggactgtgaatgtgggagtcctgggactctgggtgaagaaccgttccagaagagatgaatgagctggacaaggttctttc
atagaacctttaggcaggttttcttagaaaatgcacattgaggattatgcttggaattgtgtatgagcagaatgatactca
atccctctctgcatttggaattctctttgaaagaaaacacacacagctatttctcagagatagtgagctccagccact
ctagacattttctgtgtgtagctctacattataatctcacagcagctctctgatattgacaatgtcaaaatagcccaacctt
ctctaaacttcagagatgtctgatattgataattgaaataaaacacacacacacacacacacacacacacacacacacac
gatactttttctgcttgacaaaataacagtgagaagaactgtatctcacgtctttttctctttggaaagcctgaacacacag
aacccaaacttgaggctctctcagctatagcaattctgacttcacagctctgtaaatattgttctttttcttttagctta
tgcttttgccttaatttatcttttctctgttctaatgaattattgtcctatatctgctgtgagcttaggtgacatataa
cagcaattaaatataatgaattggtacatataaagatttgactaaaactcgatgtaaaaataagtggttctacattcaatt
ccagtgtagaaacagtgctgacttgaacagagtgacagaatttccattcttccctatttttgacagctttaaactttata
ttttcttcttcttctgtgagccgtcattaaacttttctctcaagccattcccgattaccctatcttgacagcgcagacag
atttgggaatttgcgctcagagcttgatttggacacatccccccagccacacatgagatccttttaattctattgcatattaa
ctagttttaagtacaatattcctactcattttaaaccacataatcaaagaatgagtttgaaaatgaacaaatgcaaac
tacagttagaataatgttagtgtcttttagttttgggttaggagtcggtttctgtttgtttaaactcaagattgtgaacag
ttttaactcactgttttatttccaatagagattcaggtttacatttgaattcagaacaaaggttttcttctctcattaca
gagaacactaaactctacatctcccttcccgagcaaggagctggccgaagccacacacacacacacacacacacacacac
ctctggccagagaggaattggtgtctttccagctaccaggaagcggatcatccactgtatcagtaatttccattccctgag
ctggcaagaggtccttttgagttgaatatcacatgggagtgtaatatcaatttcaaagataaagtgtatgaacaataat
gttttgatttcttatttttagaaaatgaagaaacctaaactcatagatgtctcagagctaatgggttagtggttaacagc
tggatattctagtttagaaccttctccatttttcttcttggccctaggtaattcttatttgtaaagaggagaatttct
ctgccaactgcccactgcatgcttttgtctgacacagcaatttctccatattgcttctcagtagcaagggcaatcattta
ccaaacacacatgcttgcttaactaacaggaataacgtggtacccttaattcagcccttcccttgaaagcatctgggttct
gaggttcaactatggggaatatggtctcttaataaacatttaagttgagtttgccttttaggtccacatggtgacaaatgta
tcagagtaattctctgtcctaggatcagagggcctgtaggcacttgcaaaagcagttagctctgactcccagccagtgac
actccacctttctgactcccagccttgtctcaaataggcttggaagcaggaactgtctggtgtccccagcataggaa
gctgagccagggggcagtgctcacaaacaatacagactttaaactgttaggatattggaaaaataaataatttgggggaaat
tgtctcagacttgggtccaccccttatttttagctgtcttctaataccgttttcttttttgggtgcttgatctaacctac
cattttttgggtgcttgcatcatttttcaaatatcaaaaagcaacttatgttttctaacaatgaagatttgcattgtt
cattctggaaaaatgctgaagacttggaataatcaaaaatgctgagatcaaacactattgatacgttagtgatttcttcc
tgtctgttctactttcttcttcttgaattctgtctcagctgttctgactgatgaggtctgacttttgggttcttcttca
gaggagaagccttcttctcagcttgccatttcttaccctggttatgaaggctggtaaccttttttactaggtagagaagct
ggaccaaactgggggttcttccagggggagaaagagaaagagaaactgttttgcaagtcogtagctatttctctaggccct
cttagctgacattgacatgcttggcattgcttgcagatccctcgcagccctctgtcccttggttcatcttggcccttag
agaaagcaagcaggggtctttaaaggggaggttgccttcaaaactcaggggttgggttacagctgttctcacttacatcac
tggccctgggttttttttttttcttggcattaaaaaaaaatgggaagcaggtgatgttccattgtctgagtggtggga
aactctccaaagtgaacaataacggttttcttggcagctgttcttggcctgttctgtctctgggtccaggacaagcaag
gacctctgctcttctcaatagaacacctccagatccctttgatcaaaagtactcatgtctgacttgctatttctgtg
agataaatggggagaagatcaataaatgcacttgtttgtccagtcagcgtgtggaaaggttgataattttgaccaaagcaca
accttgaagggaaaaagaaaaggagtgaaagcttcttgagaaagctgcctaggttcagacagtgctcaccatttccctgt
atgctccacatgacaaaactgagtggttctctatgctccattttgcagatggcaccagggctcagaaggggttaggcaac
ttttccagtcacccaatgagcttaattgacaaaactgggattcaaacccagaactgttggattccaaagcctgtgtgtg
cctgcttctgtgaaaaactccagtagcgactgaatagaagggagaaccttcaagaaagaaaaacgcactagcagaacc

Fig. 12
Page 11 of 30

[illegible]

Fig. 12
Page 12 of 30

gcaactttaaataaatcccatctctctctctctctctcagcttgcaagttgacccaaggaagccttcatttccatgacagac
ttaattgtgagggcatcctca

SEQ ID NO: 21

Genomic contig containing ABC1 exons 9 through 22:

[illegible]

Fig. 12
Page 14 of 30

tttgcagagaatgagttgtttttttgttttgggtttttagtaccttaacataatctacctttagtttaagtatcgctcac
agttacctagttaactgaagcaagccccaaagaaatttgggttggcaacacctttgttagcctcggtttttctctctacatt
gcatgtctcgtgaagcatggatcatacgtacatttcagaggtctagagggcctgtccttctgtggccagatgtgggtgct
cctctagcatgcaggctcagagggccttggcccatcacctctgggtcaggtgtgtctttcttcttcccttgtccttctt
ggggcctccagcttttctgCGGGTGATGAGCCGGTCAATGCCCCCTTTCATGACGCTGGCCTGGATTACTCAGTGGCTGT
GATCATCAAGGGCATCGTGTATGAGAAAGGAGGCACGGCTGAAAGAGACCATGCGGATCATGGGCCTGGACAAACAGCATCC
TCTGGTTTAGCTGGTTTATTAGTAGCCTCATTCCTCTTCTTGTGAGCGCTGGCCTGCTAGTGGTCATCCTGAAGgttaagg
cagcctcactcgctcttccctgcraggaaactccgaataagctcaacacagggctaaaggaggagaagaagaaaaaaac
caagcctctgtagagaaggggtcatacctgtcaattccctggcaatttcatccatttatagttggggaaagtggagccag
agagggcgagtgacttcccaagggtcaaccacagcgggttagcagctaaagtaggatgagagtgaggggttcatgtcttcca
gataaacacatgctcaactgtgccatgctgtcttattggtagtggttcatggcagcatctgaaagctatttttttctta
gatatattgggtggcgatttcttccaaagtttctaagaacaataatcagaaggatataattgttgcaggttagactgtct
ggagcagagggctgaaatagagtttgatgtatgggttatttatgagggctcaatacctatggaagagatggagagtcga
ggattggcgaggggagggagtgaactgtgatagggccaaacctgtggggcactctagagaatatgcagctgttgga
gttgttcttcatogagctgaaacatccagcccttctgtctccccaaaggcctcctcctgacaccacctacctcagccct
ctcaatcaatcactggatgtgggtgcccgtgggaaggtcgtgcccaggggctacatggctctctgtgtgtgtgacaaac
ccagagcttctgtatgctgagggccttactgacagctgggcaacagggttccctgaatggggactctgggagtgag
tttctgtctgaaccatacatataatattttatccgaatttcttctctgcaagcatttcatataaagacacatcag
gtaaaaataaatgtttttgaagcaaaaggagtagaagagataagaactaactaatttaatactagttacctctgttaac
aaatagttcctactgattgccaaggactgtttaaacacatcacatgggcttcttctctatctctactaaccttttaac
agacaaggaaatgagggctcaggaaggtcaaggactttattgagggcttccacagtaggatacagttcttgtctaaaagcaacc
cctcctctcatgctctgtttatctaaactgcaaggggaaggtcagtgccagaggttagtggtcccatgggtgggtgacataagagc
tgctctgagacaactgcatgctgggtgggtcctgagacatgtatcccatcagccggagataggctcaaaatattccacaaga
gtttggatgatttgggaaatgcagaatccatgctgatcaagaggggaaggtcaagttgcttggccatttcccttggctttt
agacagaaaaagttacgtgggatattatctccccagctcttctgtgtggccaccagtcatagtccttatataaggagaaa
ccagttgaaattacctattgaagaacaaagagcgaactcggccactgaaatgcgtagaagccctggactctgttgtat
tcataactctgccattattttctgcttagtttgggttaagtcacttatcttctttaggtggtaattgatcagttgcctc
atcagaagaatgaacagcattacgctctgcatctgtctctaacatgagtaggaataaacctgtcttttctgttagatc
atacaagctgagtgcttgggattgttgaggcagcacatttgatgctcttcttccctaggtTAGGAAACCTGCTGCCCTA
CAGTGATCCCAGCGTGGTGTGTTGCTTCTCTGTCGGTGTGTTGCTGTGGTGACAATCCTGCAGTGCTTCTGTATTAGCACAC
TCTTCTCCAGAGCCAACCTGGCAGCAGCCTGTGGGGGCATCATCTACTTACGCTGTACCTGCCCTACGTCCTGTGTGTG
GCATGGCAGGACTACGTGGGCTTCACTCAAGATCTTCGCTGtagtacctctggcctttcttctagtggtgttaggcat
ttgaccttctcttggagtccttgaaataaaagcagcaagttgagaaacagaagatgattgtcttttccaattgggacatgaac
cttagctctagattctaaagctctttaagggttaagggcaagcatgtgttttattaaattgtttaccttagctcttctcag
tgaatcctgggtgaaattgaaattgaaattgaaatttccgagagccagactgcatcttgaaactgggctggggatataatggca
tcaggaattgggttcaggcaacagatgccatcttggcctttatctccagctctgttggctatgttaagctcatgacaa
accaagggccacaaatagaactgaaactcttctgagcagatgacctcttctgtcttcttctgtgtccagtatgggtgtt
tgcttgagtaattgtttctgaactaagcacaaactgaggagcaggtgctcatcccaaaaattcctgacttggacacttcc
ttccctcgtagagagcagggggatatttggagagtggttgagcccttacaagtgcaagttgtcagatgtccccaggtca
cttatcaggaagagctaaagagtgactcataggatgctcctgttgcctcagcttgggcttcataggcatcagcagccccaaa
cagggcactctgacccctgagccatcttggctgagcagggagcctcagaagactgtgggtatgagcagtggtgtgsggga
acaggttgctgagccttggggcatcttggaaacataaagttttaaagtttctatgcttactgtatattgcatttctga
aatgttctgtatataatgagtggttacaattggaatcattttatattgttacttggtagccaccactccttaaagggaactc
tataggtaaatactacttctgacacttatgattgacattttgcaaatcaaatttctccaggtataatttacactaga
agagatagaaaaatgagactgaccaggaaaaggataggtgactttgctgtttctcacagAGCCTGCTGCTCCTGTGGC
TTTTGGGTTTTGGCTGTGAGTACTTTGCCCTTTTTCAGGAGCAGGGCATTGGAGTGACAGTGGGACAACTGTTTGAGAGTC
CTGTGGAGGAAGATGGCTTCAATCTCACCACTTCGGTCTCCATGATGCTGTTTGACACCTTCTCTATGGGGTGATGACC
TGGTACATTGAGGCTGTCTTTCAGGgtacaagcttgggcaattgtttggaaaatatgacttctagctgatgtcttct
tttctgtcagaatctctgcagtgcatgggttccctgggaagtggttgggctatagatcttatagttaaacagatagctcca
aggacagggcagctgagctgaaagtacaattgctactcttctacagcacttgtttctgaaaaactgtgtgccagggcagc
atgcaaaaatgtttatacacattgcttcatataattctcacaaggctactctgaagtagttactataataaccagcaatt
tcaaatgagagaactgtgactcaagagcgttaagtaaccagcttgggtcacacaactgttaaatgttggtacgtggag
tgaaatccacttgggttaactgggtcaataagccccagggaatcctcccaatgctcagcccaattctgtattctctgtgtcc
tcagaggggggtacaactaggagaggttcttctcctgagtagcaggttgttaataattaaatataactagctctaaggcctg
cctgtgatttaattagcatcaataaaaaatcatgttgaaatttcttcttagtacttcttcttaataataacatcttct
tgaccaagtccaagaggaacctgctgtgagaggttctcattagatcaaatctgagagagcaagatttaaccttctt
ggtcaccttctgatcctccctaaaggaggtatacatgaaatatttattactcctgacctgaacttcttctattgaatatg

Fig. 12
Page 17 of 30

ttgaaagcttgaactgcctgggtgcatggtggccagggctgctggaaaacagggttggaaagcgatctgtcacctttcacttt
gatttccctgagcagctcatgtgggtgctcactgttgggttacccttgaatcttgaagattattttcagaaattgataaaag
ttattttaaaaagcacggggagagaaaaatatgcccattctcatctgttctggccaggggacactgtattctgggggtat
ccagtaggggcccagagctgacctgcctccctgtcccccagGCTGACTGTGGAAGAACACATCTGGTTCTATGCCCGCTTGA
AAGGGCTCTCTGAGAAGCACGTGAAGGCGGAGATGGAGCAGATGGCCCTGGATGTTGGTTTGGCCATCAAGCAAGCTGAAA
AGCAAAAACAAGCCAGCTGTGAGgtgcgggcccagagctaccttccctatccctctccctccctctcccggtacacacatg
gggagggaaaaacagcactgccccagggctcccagggctgggtgggttggtaaacagaaacttgtccctgggtgtgccccttag
gtcccttgccttcactcactgtctggggctgggtcctggagttgtcttgcctctgttttttctgtagGTGGAATGCAGAGAA
AGCTATCTGTGGCCTTGGCCTTTGTGCGGGGATCTAAGGTTGTCAATTCTGGATGAACCCACAGCTGGTGTGGACCTTAC
TCCCGCAGGGGAATATGGGAGCTGCTGTGAAAATACCGACAGctgacctgatgtgtatttattctgagtaaatggactga
gagagagccggggggtttttgagaagtgtggctgtatctcatgacctaggcttctgtgaagccatgggatactcttctgtta
xcacagaagagataaagggtcattgagactgagattcctgagaggagatgtctgtctttatttcatcttttctgtccccaac
atgggtgcaactaaatttatgggttagttgaaagggtggatgcttaaatgaatggaagcggagagcgggcaggaagacgattgg
gctctctgggttagagatctgtatgtggtacagta:ggaggacacaggcaggcttggagccaactctgggttggccctgaga
cattggsgaaagtcaaaacttgacctcaccttcttggcgataataatagtggtgctgtacctcatagaggattaaattaaa
tgagaa:gcacacaaaaccacctagcacaaatgacctggcatatagcaagttcccaaaataaaatgcgtaactgttcttaacct
gtgaggatgtggtaacctatataacaaaagctttcccatcttaggggtcatagccatacaggggtgaaagggtggcttccagg
tctcttccagtgcttacccttgctaataatctctcttagtccctg:caactgtgacaaatcagaactgagaggcctcacctgt
cccacatccttgtgtttgtgacctggcagGCCGACCAATTATCTCTCTACACACCACATGGATGAAGCGGACGTCCTGGG
GGACAGGATTGCCATCATCTCCCATGGGAAGCTGTGCTGTGTGGGCTCCTCCCTGTTCTGAAAGAACAGCTGGGAACAG
GCTACTACCTGACCTTGGTCAAGAAAAGATGTGGAATCCTCCCTCAGTTCCTGCAGAAAACAGTAGTAGCACTGTGTCTATAC
CTGAAAAAGgtgagctgcagctcttggagctgggctgggtgttgggtctgggcagccaggacttgcctggctgtgaatgat
ctccatctccacccttttggcatgttgaaaccacctctccctgctctgttggccctttgaaatcatatcatacttaag
gcatggaaaagctaaggggccctctgctcccatctgtgctagttctgttgaatcccggtttctcttttctatgaggcacana
gagtgatggagaaggctccttagaggacattatctgtcaagaaaagagacttgtcaagaggttaagagccttgggtacaa
atgacctgggtcgttctgtctcattacttttcaatctcat:gaaccttaacttttaactataaaacagccaatatttat:ta
ggcactgatttcatgccagagacactctgggca:tgaaagaaaagtaatgataatagtttaatttatatagcgttgttaac
atttcaaccttttttttttttttaacctctatcatctcaattaaag

SEQ ID NO: 22

Genomic contig containing AEC1 exons 23 to 28:

ggaacacacattaaagcatgagaagcatgaactagacatgtagccagggtaaaggccttgctgagatgggtggcaaaaggc
cattgcagcattcatggcaggccacagttcttggcagctctgcttccctgaccttcacctcaggaagcgaaggc
ttcacacggccacacacatgccagacagggtcctctgaagccacggctgccagtgcatgtgtccagggaagccttttc
cttagttttcacacaacagagcttcttgggaagccttcccgggcgaaggtgctgggtgctctgcttgcctccgtccctga
ccggttcttaccttcttcttggccatcagGAGGACAGTGTCTCTCAGAGCAGTCTGTATGCTGGCCTGGGCAGCGACCAT
GAGAGTGACACGCTGACCATCGgttaaggactctggggcttcttattcaggtgggtgctgagcttccccagctggcga
gtggaggccagggagcaggggtgcagagggctgggtggcctgactcaaggttgcctgctgggctggggctgggtggctgg
gggtggcagcagcttgggtggcgggttggcctaatgcttggctgggtgcttggggctgggttgggagctagcaggggcag
tgcctccagagcagctgagatgattgggggttggggcaatcccttaggggagtgacactgaataccagggtgaggagctga
gggccaagccaggagggtgggatttgcagcttagtacataagaagagtgagagcccgagagatgaggaaacagcctccaga
cttttcttgggtagcgtgtgtaggagggcagtgctaccagtagcatatgtggaaacagaggttggaccttgcctatctt
ggtagtcttaaggctgggttcttccagggaaggcttctgcttccatggagctgttagattaaacctttatttaggttaaat
gagggaacctactttataagcataggaagggtgaagaatcttttaagattcccttactcaagtttcttttgaagaatc
ccagagcttaggcaatagacaccagactttaggctcaggtatccattcaccatccaccacccacccacccatccctt
cctcttccatccctccattcaccatccaccatccagctgctccaccatcttcaactgagtagcttataatgtgctgg
cttgggtgatacaaaagggtgaataagacatagcttcttcttggcccccaacctcagaccagagatgaacatgtggaatg
acctaaacacctggaacagggtgtgggtgtatgagcggcagggctctgagtagaggggtgggggtgagccagcctcactccg
aagccccctgaggttgattgagccatcttggcatcttgggtcctgcagATGTCTCTGCTATCTCCAACCTCATCAGGAAGC
ATGTGTCTGAAGCCCGCTGGTGGAAAGACATAGGGCATGAGCTGACCTATGTGCTGCCATATGAAGCTGCTAAGGAGGGA
GCTTTTGTGGAACCTTTTCATGAGATTGATGACCGGCTCTCAGACCTGGGCATTTCTAGTTATGGCATCTCAGAGACGAC
CCTGGAAGAAgttaagttaagtggctgactgtcggaaatataagcaaggccaaatgtcctaaggccagaccagtagcctgc
attgggagcaggattatcatggagttagctcatcagtttttagctcatcagatctgattaatgttggccccagctgagcc
attaaagatggtagtgggagatagcaggaaagaaagctgttctctgtaccacagtagatcagctgagatttgggtgttga
aaccagtggtacctaacacatttaccatcccaaccttaaacctcctatgcacttattaccctttaatgagcctcttactt
aagtacagtgkgaggaaacagcggcatcaggatcacttgggaacttgttagaaattcagcaacttgggcccagctcagacc
tactgaatcagaatcaggagcaatctctgggtgctgactgtgtccagcagcagctatcaactggattctccatcatagga
tgacaacagtttatggatggatagttctacttggcagggtgctgagatttcttcttgggttcttggatttcttcttaacca
ctgtgacctcatttaattctcaaaaaaagatgaaaaaatgaacactcaggaaatgctgacatgagattcagaatcaggggt
ttggggcttcaaaagtcctctctcttccatgtaatgcctcccttagagatacaacatccacagaccttgaaggctg
aaggggataataaaagctgtctggccaagtggttcccaagcttgacagtgccagcagaatcacctggggatatttataaaaa
taaacataactaagggttgggttccagggtgctgaatcagaatcttctggagggtgagggcctgaagctctgtattcttctg
atacttggacacagtggtctatagactagagttgggaatgattgcgtcattcagattctctctgatttctctgatttctg
ctgccatcatatttctagtgctctatttctctcctcctcctcctcctcctcctcctcctcctcctcctcctcctcctcct
gatttagagccacagctcctgaaagaaagccacttgactcattccctgtaggttcagaataaaattcttctcctcctcctcct
gtcatagctttttttaaatttttttttatttttgatgagactggagtttggctcttattggcccaagctggagtgagctg
tgcatatttgggtcactgcaacctccacctccaggttcaagcagattctcctcctcctcctcctcctcctcctcctcctcct
caagcatgtgctaccacgcccagctaattttggatcttctttagtagagatgggttttccatgttgggtcagggtgggtctcg
agctccagacctcagggtgacttgcctcggcctcccaaaagtgctgggattataggcctgagccacagcgtccagcca
taactttaattgaaaatgattgtctagcttgatagctctccacctgaggaatgttctctggcgaacacaggtcttctct
cccaggttaactctgagaaagtgatttaagaatgtgggtcttctttagtagagatgggttttccatgttgggtcagggtgggtctcg
aatataatatacgtggcagtggtgactactcctgtaattgttgggtgcttataatgttctcctcctcctcctcctcctcct
TTCTCAAGGTGGCCGAAGAGAGTGGGGTGGATGCTGAGACCTCAGgttaactgccttgagggagaatggcacacttaaga
tagtgcccttctgctggcttctcctcagtgccagagatttggcttcttcttcttcttcttcttcttcttcttcttcttct
agtgtaggttgggtgcagatggggaaaggttcttcttgggtgtaataaaataaaagtagggatttcttcttcttcttcttca
gATGGTACCTTGCCAGCAAGACGAAACAGGCGGGCTTCGGGGACAAAGCAGAGCTGTCTTCGCCCCGTTCACTGAAGATGA
TGCTGCTGATCCAAATGATTCTGACATAGACCTCAGgttctgttggggcaagatcaaacaggttcttactgttgaatgtga
aattctctctcatgctctcactgttttcttggatggccttagccaaggtgagatccctacagagtcctaaagagaa
ggtgaggaatggtaaaagccactgttcttggcagctctgctgactgtgacaaacctgaaagagcctatccatctcactt
cctttaaagacataaagattgggtcctcaatctctgaacccatgtatttattatcttcttctcgggggtcctagttcttgg
tatacattaggtgtttaaattcttgaacaaatattcattcgagtagatgagtgatttgaagaggtcagaaaggggaattt
gctgttagagtttaattgtaccttaagacttagatatttgaggtgggcatgggtggtcctatgagtaatccagcgttctt
gagaggtgaggtgggttagatcacctgaggttagaggtttagaccaggtctgaccaacaaggtgaaaccccgctcttact
aaatacaaaaaatttagccagctgtgggtggcagatgctgtcctcagcctacttgggaggtgagggcaggagaaatcgctt
gaacccaggagggcagaggttagctcagctcaggttggccttggccttggcctcagactccagactgggcaacaagagtgaaacacccat
ctttaaagaaaaaaagcaatttagataattggatgagtggtgtcttctgtgtctttaaactagatggagaggagagctt

Fig. 12
Page 19 of 30

SEQ ID NO: 24

Genomic contig containing ABC1 exons 30 and 31:

tcttggcagtccttactcattttttcagcacatcgagcataagatccagactcttcccaggcctctctcatctggctcct
ctctcctcctttatcattactctcttcgtagcttatcctactccagccatgctgtcttcttattatcctaaaaarta
gaaatgcatttcttccagggccttctgtacctgcacttggccatctcttctcagaaatgttctttttgccaagcttttg
cccagcttgttctccatcattgttatgttttggctgaaatgtcttctttagtagcttccattctcccagtcactgtctt
tttatttctcttatttttgggcccattcaagggtatcttatttagtgatttgttgttctgtctcctccatgggcatacacct
ccatgaaggcagggtattttcaccttagggcctcgaatatactggacagcatctggcacgtagtagatgtcacaagaaatgt
ttgttctcagcaaaatgggttgggtgattggattgaactgagttcagtatgtaaatatttagggcctctttgcatctctat
tttacttatgtataaaatgatataaatgatgataaaatgatgtcacagtgtaacaaggctgttgtgggatacaagcaatc
aaatgagatcatgttcttcttccaaatgggtgaggggaatagatgcatgttctgtgttgttacgggaatgatcctgtgctc
ctgagggcaacagaaaggccaggccatctctggtaatcctactcttctgtgtcttctcttcttgcagAGACACGCCCTGCCAGG
CAGGGGAGGAAGAGTGGACCACTGCCCACTTCCCGACCATCATGGACCTCTTCCAGAATGGGAAGTGGACAATGCCAG
AACCTTCACCTGCATGCCAGTGTAGCAGCGACAAATCAAGAAGATGCTGCTGTGTGTCCCCCAGGGGAGGGGGGCT
GCCTCCTCCACAAgtcagtcactttcaggggggtgttggggcagaaggggtgcaggatggggctggtagcttccgcttggaa
gcaggaatgagtgagatcatgttgggggggtctgtttcagtccttttttgttttttcttctgaggcgggagtc
ttgtctctgcgccaggctggagtgctgtggcatgatcttgcctcactgcaacctccacctccaggttcaagcgattct
cctgcctcagcctcctgagtagctgggattacaggcagcaccaccatgtctggctaattttgtgttttttagtagagat
aggggttccgctgttgggtaggctggctctggaattcctgacctcaggtgatccacctcgccctcggcctcccaagtgctg
ggattacaggcgtgagccactacgcccagcctcttctcagtccttaactcgttcttctgtcataagaaaaagcatgtgagtc
tttgagggggagaaggtttggaccacactgtgcccatgcctgtcccaagcagtaaaagtcacaggacagactgtggcagggc
ctggcttccaatcttggctctgcaacaaatgagctggtagccttgcacaggcctgggctgttcttccactctgaaatga
gggaggtctggaccagaaaactcctgtggatcttctcaactctggtattcttagagactctgtttgggaaggagtcctgag
ccattttttttcttgagaatttcaggaagagcagtgcttatgtagctctctgctgcttttatcagcaaccaaattgc
aggatgaggacaagcaattctaaatgagtacaggaactaaaagaaggcttggttaccactcttgaaaaataatagctagtc
caggtgagggggtggctcacacctgtaatctcagctattttgggaatgcccaggtggactgatcacctaagggtcaggagttcg
aaaccagcttggccaaatgtggcgaaacctgtctctactaaaaattcaaaaaatagccagccatgggtggcacatgcttct
aatcccagttacttgggaggtctgaagcaggagaatttcttgaacctgggaggtggaggtcgagggagccaaaattgcgc
cactgtactccagcctgagcaacacagcaaaaactccatatacaaaaaataaaatgaataaaataacagctaattctagtcat
cagtataactccagtgaaacagaagatttattcagccatagtgaaatgatgggtcttcttaaaaaatctcttgactacaaaagaa
tctcatttcaatgtttattgtttagatgttcaaatataattcttgggaaagaccttggcttgggtgtaagtgaattaccag
tgccgagggcagggtgaaccaagtctcagtgctgggtgactgagggcagtgctggggacctgtagttaggtttccggtca
cactgtggacatgggtcactgttgtccttgatttgtttctgtttcaattcttgtctataaagacccgtatgcttgggttt
catgtgatgacagAGAAAACAAAACACTGCAGATATCCTTCAGGACCTGACAGGAAGAAACATTTGGGATTATCTGGTGA
AGACGTATGTGCAGATCATAGCCAAAAGgtgacttttactaaaacttggcccttgccttattattactaattagaggaat
taaagacctacaaataacagactgaaacagtgggggaaatgccagattatggcctgattctgtctatttgggaagtttagga
tattatcccaactagaaaagatgacgagaggggactgtgaacattcagttgtcagcttcaaggctgaggcagcctggct
agaatgaaaaatagaatggattcaacgtcaaatcttggccac

SEQ ID NO: 25

Genomic contig containing ABC1 exon 32: _

gcatgctggagtgatagtgacccatgagtttctaagaaagaagcataatttctccatatgtcatccacaattgaaatatta
ttgttaattgaaaaagcttctaggccaggcacggtggctcatgcctgtaatcccagcactttaggagccaaggcgggtgg
atcacttgaggtcaggagtttgagaccagcctggccaacatggggaaccctgtcttactaaaaatacaaaataagctg
ggcgtggtggtgctgctgtaatcccagctacttgggaggctgaggcagsgagaactgcttgaatctgggaggcggagggt
tgcagtgagctgagttcatgcccattgcattccagcctgggcaacaagagcgaaaccaatctcccaaaagaaaaaaaaga
aagaaaaagcttctagtttgggtacatcttgggtctataagggtggtttaaattgggttaaccaaggcctggttctcat
ataagtaatagggtatattatgatggagagaaggctggaagaggcctgaacacaggcttcttttctctagcacaaccttac
aaggccagctgattctagggttatttctgtccgttccttatatcctcagggtggatatctactccttttgcattcattagga
ataggctcagtgcttttcttgaactgatttttcttcttcttctgtctctgcagCTTAAAGAAACAAGATCTGGGTGAATGAGT
TTAGGtaagttgctgtcttcttctggcacgtttagctcagggggaggatggtgttgtagggtgtgcttggattgaagaaagcc
tcggggattgtttgtcactcacacacttgtgggtgccatctcactgtgagga

Genomic contig containing ABC1 exons 33 to 36:

gctttatagagctttctgcttagagcatcatggctcagtgcccagcagccctccagaggcctctgaatatttgatatact
gatttccctgaggagaaatcagaaatctctgcaggtgtctagggaattcaagtaagtagtgttgagggggaatacctac
tctgactttcccccaaacagatccccgaggcttcttaaggactcaaggacaattcttaggcatttagcacgggactaa
aaaggctcttagaggaaataagaagcgccaaaaccatctctttgcactgtattcaacccatttgcctctctgggttttga
aggaacaggtgggactggggacagaaagagttcttgaagccagtttgcctcatcggaataatgagataggtgatgtggcta
cgtcagggggcccgagggtctctgttactgattccgtctttctctgctttttccccaaaggggccaggacccttgga
tctctggccagagcagacgcagggccctataatagccctcagctcagaaaggagccggagcctgtgtataaggccagcgc
agcctactctggacagtgagggttccactctcccaactccccatctgcttgcctccagaccacattcacacacgagc
cactgggttggaggagcatctgtgagatgaaacacattctttctcaatgtctcagctatctaaactgtgtgttaactca
ggccaggtcctcctctgctgggcagaaacattgggagttaagagattgccaaactttattagaggaaagctgacgtgtaact
tctgaggcaaaatttagccctctttgaacaggaaatttgacactgaaaccttgacacactgcactgagctctgctgct
gtgatactctgtgcacccccactgtctgggttttaattgtcaggtcttcttttaggtatggcggttttccctgggtgtcag
taatactcaagcacttccctccgagtcagaaagattatgatgccatcaaaccaatgaagaaacacctaaggtggccaaag
caaaatactctatctgaagatgtatcagaaaaatgggcatgtagctgctgggatataaggagtagtgggcaggttaaacga
tcacctggcagctcattgttctgaatatgttgccatcacagagcctctttggcatttagcgatttgagccagacaaaaact
gaattacttagttgtactgtttaaagtgtaggtcaaaaaacaaatccagagccaggagctgtgggtcatgctgttaactcc
tagcacttggggaggctgaagcgggtggatcacttgaggtcaggagttcgagaccagcctggcctacatgacaaaaacccc
gtatctactaaaaatacaaaaaaattagctgggtctgggtggcacaacactgtaatcccagctacttgggaggttgagcca
ggagaattgcttgaacccctgtaggaaagaggtttagtgagccaaagatcgacccgttgcaactccagctgggcaacaaagag
caaaaactccatctcaaaaaacaaatataatccagagatttaaaaagctctcagaggtggggcggtgggttacacctgtt
atcccagcattttgggatgctgaggcgggcaaaagcacaaggtcaggagtttgagaccagcctggccacatagtgaaccc
ctgctctgtcaaaaaacatagaaaaattagccggcctggtggcctgcccctgtaatcccagctactcgggaggtctgaggt
tgagagaatttcttgaacccgggagggcgaggttgcagtgagccagattgcaccactgcaactccagcctgggagcagaca
gcaagactccatctcaaaaaagctctcagaaacacacaggtttcaaaatttgggtcagttgggtaaataaactgggtttcaa
acatacttctgctgaayaatcactgactaaataggaaatgaatcttttttttttttttaagctggcaagctgggtctg
taggacctgataagtaactcactcattttctctgttctcaggttccccatttttaggtgagaatttaagggtgtctgtataa
aacagaccttaggatttgaggacagcagtgatagctccagagtcacaaagctctgcttttaggtgatgggccccatgtatctg
gcacatctgcaggcagagcgtggttctgggtctccagatgatgctgggtggagcacttgaggagctcctacccccaccgtg
ataaccagacattaaaaatcttggggctttgcatccagagatttctctgtgattccttctagacttgggtcatctggcag
catcactgtctgtagatttctagtcacttgggttccaggagccgttatttaattgggttccacatttaatttcagtgaaacaa
ggtagtggtcattgctcttcacaggccggtctctgttccacaggttccagattgactgttggcccttctatgtgaaaca
gtcacaactgaggcaggtttctgttgtttacagGACAGTTCTGCAGATCGATTTCTCAACAGCTTGGGAAGATTATGAC
AGGACTGGACACCAATAAATGTCAGGtaaaacgctgtcttctgttcttagtagctttttgtatgaacaataatccttatg
tttctggagtgactttcaactcatggtaaggttggcaggggcatccacaacagaaaagagcaaaactattaaactttaccag
tgaggcagtagcgtgtgtagtgattcagagaatttgccttggccaccagacataaccaggttaaccttgactaagttact
taacctatctaaacctcagtttccctcatctgtgaaatggagacagtaatacatagctatttccaaactgttgtagaattc
aatgagttaaaaggtataaggtcctccacacagcgcctggccacatagtcagtgatcactatgtcctgaacactgttaatta
cttcgccatattctctgatcatagtggtttgcttgggtatgtgactagaatttcttcttgagggtttatgggcatgggtgg
tgggtatgcacctgctgcaggagcccggttgggggcttaccctgtacctgggtatgtttcttctcaggtgtgtgttcaa
TAACAAGGGCTGGCATGCAATCAGCTCTTTCTGAATGTCATCAACCAATGCCATTCTCCGGGCCAACCTGCAAAAGGGAG
AGAACCTTAGCCATTATGGAATTACTGCTTTCAATCATCCCTGAATCTCACCAAGCAGCAGCTCTCAGAGGTGGCTCTg
taagtggtgctgtgtctgtatagatggagtgccggcaaggagaggggttatggagaaggggagaaaaatgtgaatctcatt
gtaggggaaacagctgcagagaccgttatattatgataaactctgatttgatccaggctctgggcagaaagtgataagttac
gaattgggtgggttgggtctctgaactgcagaaagagaaatgacactgatatgtaaaaaatcgtaaacatttagtgaattca
tataaagtgagttcaaaaaattgttaattaaatataaattcaattaaagtgcttaactcagtttgattgtttaaaaacca
ctgttttaaatttgggtggaatatgtttttattagcttgatctttaaattccataaattaaagctgtgtgtgtgtgtgtgt
gtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtgt
atacagatctgggtttgaatctgggtctctaaactttatagatgtatgatattaaatgaggcagttcatgtaaattgccaa
gcccagcactcagcacagagctgatatttccacacacattagatacctttctgtatgtggagcatggcagttcctgtctc
tgcttactcctacaggatactaatataggacactaggatctttataccaagaccctatgtaattgggttatgagaccat
tcttcttataaaaaatctgacagaatttttgcattgtgttagatcaataggctgcatactgttattttcaagttgatttaca
gccagaaaattataatttatttgagtagttacagagtaattttctgtctctatttagttttcaagccccactagtccttt
gtgtgtgaaaaatttacaacttactgtctcttacaaggtcatgaacagtggaacaaagtgaaatggcatttaaccactctgact
tcttctatttagttttatgtgacagtggaactctttgacctcagtaataaccagtttggcatttacattgtcatattttta
gacttaaaaatgatcatcttaacctgaataaaatgtgtctgtggaacagatgttttctctgggtgtgctcagatatac

Fig. 12
Page 24 of 30

Genomic contig containing ABC1 exons 37 to 42:

```

aaattactctgactgggaatccatcgttcagtaagtttactgagtgtagacaccttggttgactgttggaagacagaaa
gggcatgtagtttataaaatcagccaaggggaaaatgcttgctcaaaatgtattgtcggttatttgattaatagtttatg
tggcttcattaatcagagttactctccaatatgtttatctgccccttcttgctgataatgggtgaaaacttggtgatg
cattgtatatattgatttaggggtgaactggatgctcttctgttttacttttagTGCAATTACGTTGCTCCCTGCCACACTGG
TCATTATCATCTTCTATCTGCTTCCAGCAGAAAGTCTATCTGCTCTCCACCAATCTGCTGTGCTAGCCCTTCTACTTTTG
CTGTATGGGtaagtcacctctgagtgaggagctgcacagtggataagtcatttggtgcccagtggtcagaaggagggcag
ggactctcagtagacactttatctttttgtgtctcaacagGTGGTCAATCACACCTCTCATGTACCCAGCCTCCTTTGTGT
TCAAGATCCCCAGCACAGCCTATGTGGTGCTCACCAGCGTGAACCTCTTCATTGGCATTAAATGGCAGCGTGGCCACCTTT
GTGCTGGAGCTGTTACCGACAATgtgagtcagtcagagagaaactcctgctgggatgagcatctctgggagccagagg
acagtggttaattgtgatcttattccacttgctcagtggtattgacactgctgactgacctgctctgctctcagagtcctgt
cttccctgagaaggcaagcaccctttcttctgctgctgcttaccattttgctgggtcaagcctttcagtttcttttgaca
gttttttttacttttcttttttcaatgttgcctttaccagagtagctcctctgcttccactttacacatgagagct
gggcsagcctcagtccttaaggcttttaccatccctcctggtgtttttatgtcatctctaagatcaatgcttcta
gccttgatcataaccttgaactctaatctcaaatctcacttgcctagtggattgctccatttagatagatatagatac
cccaacctggatattgctcctagtcttctttcccttggaaacttaattgctttcttgccatccctgtcacactcagtgccac
taccatccactcgggttgcccaagctggctcttagagttatcctagatgcttgcttgctgttgagatttccacactca
actggttatgttgctcagttcttccaggtatggacctctcaaaaagggcttctctccattccgggtgtcattgaccttct
ccaaacacagcacacaaggccttttacagttgcacaaactcttctgtccataccaccacaccccttcccagctgtaagc
ttcagatgagttgctccaaccacatgctcctgtaggcctggctgaaatgcccttctctgtcacagggtctggttagt
atatcctctgcccctcaagatttagctaaaaatgtgaagcttcttacctgctgggaggtgttctctcttctctctgct
ctcagagtccttagtccatgctcctcagtagcaacgtacatcccttaccatggttaattctctgtttacatactttctctac
tcggagtgagtgctgttcttcaataattttgcctctcctccatgctcctagcacagtgcatccagcgtatagcccttattca
gtcggtagatatttgccactggttgcttctggtgagcataagctctgatgtatttgagaagaaattctcaaaatcttgaca
aaactcctgaaactcaaatatttgaccagacatgagcaatttgccttttcaaatgctaagggtatttctaatggatttgctt
aattaaatctagcctgtttctaaagcttattcattatttctctatactcagagcatttctccagatttctcaagaatag
aattttattgtacatatcatcagctatgcttctgctatttcaattgggtatctgaattaaaagggtctgggttgtctctag
agaatcaaatttttctcactcccatatttccagaacttgatacatttttaggataaaacctgaatgacacccgttctt
ctccctcaccctccctccctcccttttttttttttttttttttttagAAGCTGAATAATATCAATGATATCCTGAAGTC
CGTGTCTTGTATCTTCCACATTTTTCCTGGGACGAGGGCTCATCGACATGGTGAAAAACAGGCAATGGCTGATGCC
TGGAAAGGTTTGGtgagtggaagcagtggtgctgtaggatgctttaaaggagatggcactctgcataggccttggtacctga
acttgcttttggaagaaagcaggtgactaagcacaggatgttcccccccccatgcccagtgacagggtcatgccaac
acagctgggttggtgagctgggttttgtagacacaaccttctgctgtgtctttagagcattgagaaaagtgaaggscagt
tttgaaaggtaaaggaaaatagtggtatttgcttggatccactggctcatgcccactgtctgggttggttagaagcactggaa
aagtcacaaaccataactttgagaattagtgatcagggaatcagaaggaaagatgcaaaacttggctcttttagggcgaatc
atgtgcttcagatgaggtcattttattatcttttacacagcttataaaattataatgtattacatctttttctacctta
gaatgggttaaaaatatttctccggtagccatatgattattatcatccattagataatatagtcacaaatgggcatgcttat
ttactgttcatagaagagggtctttttgcaactggggtacaaaggagatattgaaggaaatttaaggaaatgggtacatgg
aactagatttaattgaatctagtggtttaattgattcactaggatatactgctactgaaagggaatctgcttaaaagtgt
ttctgatatattattattactaaaacttagaaattattaaaaaactactgactgtgaaaattacttgggtcggtttgcttttt
aaaaggatttttggcatgtctcattaaaaaaagaaatactagatatcttcagtgaaagtacaaatcgaatacacatgggc
tctgaaattctgattgatactgggtcataaaaagttttccccaaatcagacttggaagtgatcactctctgttactctt
tttctctgtcatgggtgatatagccatttggcttatttgaagatcggtgaattttaaaggaaacataggcccaaatttagg
aaggcccatgggttttttgatccctccattctgaccggatcttctgcatgtgcttactagGGGAGAATCGCTTTGTGTCAAC
ATTATCTTGGGACTTGGTGGGACGAAACCTCTTCGCCATGGCCGTGGAAAGGGGTGGTGTCTTCTCTCACTACTGTTCTGA
TCCAGTACAGATTCTTCATCAGGCCAGGctgagctttttcttagaaccctggagcactggttgagggtcacagaggag
gcgcacaggggaaacactcaccatgggggttgcattgaaactgaactcaaaatatgtgataaaactgattttctctgagtgtg
ggcatcccgagcccccctccctgcccattcttgagactgttgcaagtagctttataatactacgttagagactgaatctt
ttgtcctgaaaaatagtttgaaagggttcatcttctgtgttttcccccaagACCTGTAAATGCAAAGCTATCTCCTCTG
AATGATGAAGATGAAGATGTGAGGCGGGAAAGACAGAGAACTCTTGATGGTGGAGGCCAGAAATGACATCTTAGAAATCAA
GGAGTTGACGAAGgtgagagagtagaggttacaatagctcacttcagttttttcagctttatgtgctgtaaccagca
gttgctgacttgcttaataaaagggtcatgttccccaaaatgtacatctataccaaggttctgtcaatttttatctaaa
aacaccatggagacttctcaagaattcttactgagaattctttgtgatatgaattcccatcttcgaatacttgggtt
tatatgcttacatttatgtgttagttattaaaacatactaatattgtatatctagtcacaaactgagtagagagataatgggt
gatt

```

Fig. 12
Page 26 of 30

SEQ ID NO: 20

Genomic contig containing exons 42 through 45:

ttttaaaatcacctgcaatatacatatgttgaatagatgaaaaattatgtagatgataatgaatgatcgggttctaaaa
agacagggttaaaaaagtaagttcacttttattttgagcttcagaatcattcagaagccagtcgccacaaacgcagaccaag
gctcttggcacatcaaatatgacctaggcttaggggttatgacaagctctatgttcagtgatgtggtttatagtcctg
ccttccacagtttgcttgggagagctgtgagtcactcaggcttatgaatgtttacattttgcttggttgcagATATATAGAA
GGAAGCGGAAGCCTGCTGTTGACAGGATTTGCGTGGGCATTCCTCCTGGTGAGgtaaaagacactttgtctatattgctgt
tgtccctatagttcagactatctctacccaatcaagcaacgatgctcgttaagaggtaaaagtggaattttaaaggcttc
tgtatttatggcagatggagcaattagtcacgagagagagggaccctgtatgtcaagagaatgatttcagagaatcc
aatacaatttaagaaaaagcatggggctggggcagctgattcactcctgtaatcccagcactttgggaggccgaggtggg
cggactcacgaggtcaggagattgagaccatcctggccaacatggtgaaaccccatctctactataaaatacaaaaattag
ctgggcatagtagtgcattcctgtactccagctcctcgggagctgaggcaggagaattgcttgaacctaggagggggga
gggtggccagattgcgctgctgcaactccagctcctgggtgacagagtgagactcatgtcaacaacaaaaacagaaaaagcacg
cacatctaaaaacatgcttttggatccattttggatggtgagatcacaatagtttttaaaaatagattttctcctt
tctgggttccgtttgtgttctttatgaccttttggcagagtaggtgggtgcaatttgggtagctgggtttcattactgtt
tttcaacatataactttggcctcaacttgacaactcaaatataatatttataaaatacagccacacttaaaatgggtcccata
tgaaatacatatttaaatatctatacagatgtgttaaaaccaagaaaaataatttgattcttctctgtatatttaagaattgaa
gggttgaggtagttacgtgttaggggcatttatattacgttttagagtttgcttatacaacttaattcttctcttttca
GTGCTTTGGGCTCCTGGGAGTTAATGGGCTGGAAATCATCACTTTCAAGATGTTAACAGGAGATACCACTGTTACCA
GAGGAGATGCTTTCTTAACAAAAATAGgtgagaaaaagtgagctgtgtattttgctgcaagagactttgttttaattta
tttaagaaatagggtgtttatttttgattacagctggtatttttagagttcataaaaaatgttgaaatatagtaaaagggtaa
agaagcacataaaatcatccatgatttcaatatctagagataatcacaatttaccatttcttctcagtcctcattctctct
tttaacagctttattcaggtataatttacatacaataataatttgcctgttttttaagagtataattttagtgatttttggg
aaattgagagttttgcaaccatccacacaattccagtttttagaacttttccatcaccacacatctgtcttatatacacata
taaatgtgccatacaattgagatcactgtatgtagaatttaaaatagtttttattgttaatgagtgatttatgaata
tttccagtggtttacatttcttaagatgtggaatttaccattgctacataaaatccccctatgtacatgtacctataat
ttatttaataaaatttcttataaaatgttggaacacattgcttccattttcactatgtaaatatgtccctgtatacatctt
ttattatttctcaggaacaaattcttacaagtaaatgccccctctttaaagagcatatacaattgactgagccaccgttag
gccattttctgagactgacacaggtcacaaagcaattctgacttttgggaaatagactacattttataggcttcttagataa
tgttactctaaagtactttaaatatgtggggcttctctgggcttttttttttgagacggagtttctactcttactgcccc
ggctggagagcaaatggcgcgaccttggctcactgcaacctcggctccaggttcaagcgatttctcctgctcagcttcc
tgagttagctgagattacaggtgccccgccacaatgcttgcctaattttttgtattttcagtagagatgggggtttcaccat
gttggccagactggtctcagactcctgacctcaggtgactccacctgctcagcctcccaagttctgggattacagccat
gagcctgctgccccggcttctctggacttattatgtggagagatagtaaggcagtggttttcagagttttttgacct
gacctgtgtgggaaatacattttatatctcaacctagtgatgtacacacagacatgtagacacatgtataacctaaagttt
cataaagcagtagcttactgttactaattgtagtgcacttgcctatttcttattctaccttatactgctcattaaaaaag
tgcgtgctatgaccactaaattttatttcccaaacactaatgaacaatgactcaaatttgaacacactggacaggggg
atagccaataaaaattgaaaagagcaaggaaaattaatgtatttcattgatctcctctcctgtctcttaccatttttgagtagc
aatgtaaaaggaatcctaagagaacagacattttgggaatagcaggcctagcgtgacacaactgctttcctaggcttgctc
ctagtaccaagctcctgacgcataatagcagtgagcagtaataaccagcccatagtaagggtttgtcacagggactggtgtga
agaactgatttgrttggtatagctgtgagggcctggcagcgtgtccactgtgctcactcaatcctaatcttgaaaaaggctg
acctgggggtgctaattagatacacagagaggaattgaattgctgacagaggccaagttcatggcaatgcccgtctgggt
gaggtgagtcattcagttctggaaactgaacactgaactttcttccatgtagttcttccactgactggcttcatagaacc
ccaaagccacccaccaccacataaatgtgtcttaggtttgtgtgtgtcacactcaaaatttctgggcttcttctatt
tggtgcatgtgaattggtgcatatgagtgaaattctaggatggggctttagcgttaaagccctggggtagtgactgagat
tgttggttaagaaatgtgcagtggttggcatgacctcagaaattctgaaatgggactgcacctgcagactgaagtgttcag
agagccaggggaggtgcaaggactggggaggttagagccaggaaacctgcttggcaggaagagctagcatcctgggggacag
aaaggctgtgctttcaagtagcagcagatgtattggtatcttgtaatggagaagcatactttacaggaacattagccca
gattgtcttaaccagagtatctctacctgcttaaaatcttaagtgttttctgtcctttgagTATCTTATCAAAACATCCA
TGAAGTACATCAGAACATGGGCTACTGCCCTCAGTTTGATGCCATCACAGAGCTGTTGACTGGGAGAGAACACGTGGAGT
TCTTTGCCCTTTTGGAGAGGAGTCCCAGAGAAAGAGTTGGCAAGgtactgtgggcaacctgaaagccagcctgtctccttt
ggcatcctgacaatatataccttatggctttccacacgcattgacttcaggctgttttctcctcatgaatgcagcagcac
aaaaatgctggttctttgtatctgctttcaggggtgaaaacctgtaacgggtgggtggggcagggctgggtgggagagagggga
gtgctgctcccaccacacagagctccttctcctgctttggctcctcaccagttgtcaggttatgattatagaatcttagtc
ctactcagtgaaagaactttcatacatgtatgttaggacagcatgataaaatcccaagccagaccaaagtcagggtgc
ctctcactcagtagggttgggtgagtgggcctatttggaaactgggctcctgTGAAGTATGGAGAAAAATATGCTGGTAACTA
TAGTGGAGGCCAACAAACGCAAGCTCTCTACGCCATGGCTTGATCGGCGGGCTCTGTGGTGTCTGTGctgagataaa

Fig. 12
Page 27 of 30

ctgtggatggaaaactgttgttctggcctgagtggaaaacatgactgttcaaaagtccctatatgtccagggctgttgcac
gattggcttgtcttccccagggacagcagagcaaccttggaaaagcagaggggaagcttctcccttggcacacactgggg
tggctgtaccatgcctgcagatgctcccaaatagaggcactccaagcactttgttcttagcgtgattgaggctggatat
gtgatttgatcttctctggaaacattcttctaatcatcttctgtgttcattccctgaaaatgaagagtgtggacacagct
tlaaaatccccaaggtagcaactagggtcatagttccttacacacggatagatgaaaaacagatcagactgggaagtggcc
cttgaccttttttcttctgtagataagagcattgatgttattacgggaagaagcctttgaggcttttatgtattccacct
cggctctggaatttgttctgttaaggctaacagttgcaatatactagggtaatctgagtgagctggaattaaaaaaaaa
ggaatttcacccaatcttatactgacttcaatagagggtttcacacaaaaagttgttttgat

Genomic contig containing ABC1 exons 46 to 49:

ngccnngttnaaaangaaaaatctnnnnnaaatctnaannttannngnsnnntctccccagaaaaaacnaaaangattccn
ccnngggggggccccnnaantcnaaaaggccccctctntttgngngagagggaagnttttttgggaatttttaatttttgg
tcccccaaaagccctattattgagaatttaattacataaaaaagctactcagaatatttgagcttccctgcatacaataagacat
ttataataatgacctgtttacaaatgaattgaaagttactctaatctttgattcatcagaataactagaattgcca
agttaaaatttaagctgtttcaaaagatgcttctgcattttaaaacaaatttactcttgattttttttccccagcaaat
aagactatttttacttaattacagagTGAACCCACACAGGCATGGATCCCCAAGCCCGCGGTTCTTGTTGGAAATTGTG
CCCTAAGTGTGTGTC AAGGAGGGGAGATCAGTAGTGCTTACATCTCATAGctccgtagtaaaagctcttggggtccctcactgt
gggatgttttaactttccaagtagaattatgcatcatctttgtaaaaaatagaaaaatacagaaaagcaagagataaaacaa
ttatctacctgaaattatataatgcatattcttcaaaaaatgcaagcccgtagtaaaatactgctctttttactttaataata
tgtaaaaacattattccaagtcagctgcatctttagtgctattcttctatagctggatagattcccataggatatactcttatt
taactattcccccttttgtagacatttggattatttcccaacttgttcacaattgtaaacaccactacactgaagcagcat
atccctataatccacatgtacttgtaacagaaatacaattccccaggaagctgggaagtctggtagctgggtgtcttca
tgggtacagagaattctcttaaaactaaaacctcttctgttttcccgagTATGGGAAGAAATGTGAAGCTCTTTGCACTA
GGATGGCAATCATGGTCAATGGAAGGTTTCAGGTGCCCTTGCGAGTGTCCAGCATCTAAAAAATAGgtataaaagataattt
ctttgggtagtgccttagtgagaagctttagatatttattcttttgtgagtatataaatgggtgcctctaaaaataaaggsgaa
ataaaactgagcaaaacagtatagtggaaaagatagagggtttgaagtccgaactgcattcaaatctgtcttaccatt
tactggttctgtgactctggggcaagttacttaactactgtaaagcttagtttccccgggaagattctactcttagcttctg
tgctatagatgaaatgaaaaaaatttactgtgtccagctactggtgagagcgcaagcttctggagtc aaacacaaaatggstt
tgcattctggcctaccattatgagctctgagccattgggcaagtgactaaactccccgggctcagtttctctgttaacaaat
ctgtcagacttcatgggtccaggtgaggattaaaggagatcatgtatttaccagcatggcattgggtcttcacataaaat
aagattattagtaaatgataactggttctctctctcagaaaactatttctgggctgccagggggccgcccccttttcatggc
acaagttgggttccccaggggtcagttattctttaaatagttttctggagatctctccatttgggtatttttctctgtctc
agGTTTGGAGATGGTTATACAATAGTTGTACGAATAGCAGGGTCCAAACCCGGACCTGAAGCTGTCCAGGATTTCTTGG
ACTTGCATTTCTGGAAGTGTCTCYAAAGAGAAACACCGGAACATGCTACAATACCAAGCTTCCATCTTCATTATCTTCTC
TGGCCAGGATATTCAGCATCTCTCCAGAGCAAAAACGCACTCCACATAGAAGACTACTCTGTTTCTCAGACAAACACTT
GACCAAgtaagctttagtggtc caaaacagatttacttctcaggggtgtggattctctgccccagacactccccgccataggtc
caagagcaggtttagtatcttgaattgtgtcttgaattctctgattctactattcttagctatgcttttacttaaacctctctg
aacctgaaaaaggagatgatgaccttagtactcttaggatttagtgagaatttactgtataataaccataaaaaactac
catttagtgagcacctcatgactgggccaggcatcttacttgggtccctaatcctattttaattagataaaaaagttaccaaat
aggctctgacacttaagaaagtagtactcagtaaaatttttctcccccttccccctttaatcaagacggtatgtgccaagstaaa
tggatgactgagcagttgggtgagtgtaggggtggggggcgatagaaaagtcagtttttggccggcggtgggtctatgc
ctgtaattccccagcatttgggaggtgaggaacaggcgagatcatgaggtcaggagatccagataaactctggccaacagggt
tgaaaaccccgcttctactaaaaatacaaaaaattagctgggcatgggtggtgcgcacttgcagtccagctacttggcaggc
tgaggcaggagaatttgcgcgaacccaggaggtggagggttacagtgagccaaaggtctcgccactgcactccagctcgggga
cagagcaagagccccatttcaaagggggaaaaaaagctctattttaaagttgattctgttttcaaagtattcttcccccc
ttcacacacagttttttagtttaattcattttagtaattctgtatgctcctacttgacctaatttcaacattctggaaaaaat
agaactagaataaagaatgagcaagttgagttggtatttataaaaggtccttaattctttaaagctATTGTGAACTT
TGCCAAGGACCAAAAGTGATGATGACCACTTAAAGACCTCTCATTACAAAAACAGACAGTAGTGGACGTTGCACTT
TCACATCTTTTCTCAGGATGAGAAAGTGAAGAAAGCTATGTATGAAGAATCCTGTTTATACGGGGTGGCTGAAAGTAA
AGAGGAACATAGACTTTCTTTTGACCATGTGAAGTGTGTGGAGAAAAAGAGCCAGAAGTTGATGTGGGGAAGAAGTAAACT
GGATACTGTACTGATACTATTCAATGCAATGCAATTCAATGcaattgaaaaacaaaattccattacagggggcagtgctcttg
tagcctatgtctgtatggctctcaagtgaaaagactgaaattagtttttttactatacctatgtgaaaactctattatgs
aacccaatggacatattgggttgaactcactctatttttttttggttctgtgattctcatttgggggtgcaacaa
taattctcaagtaaatcatggccagcgatatttgatacaaaatacaaaaggtaatgcacatctcattcactaagccatgcc
atggccaggagactgggttccccgggtgacacatccattgctggcaatgagtggtgccaggttattagtgccaagttttca
gaaagtttgaagaccattgggtctgtcatgtcttcttttgaagctctctgtcagagcttatcaacattgaaatca
gttgacagaaattgggtggcgtgggttaaattccctgcttttattccctctgataagctgtctgtgggtgagcaaatgcga
acaaaaatgtgggtgtctccaggccacgggaaacttggctcttcttattgttatattgtcctatgcttcgagccatgggtctaca
gggtcatcctctatgagactcttaaatataatttagatcctgttaagggcaagaatacaacagccaactgtgggggtgc
aactctgtgaagccagggtcattgggattaaagagattgtggtctcaaaccttaggggaagcctgtgcccatttgtcctgactgt
ctgtcaactatggtacactgcattcagaatttttattcttgacacaagtggtatttcttggcttttttgaatttaattcagaa
aatgaaaagatggagttgtatttgacaaaaatttctgtacttttcaatgtttatttggaattttaaagttctatcagtgaa
ttctgaaactcttagaatggccctcttgtgtaaaccttgggtatagaggagtagggcactggccactccccatttttattct
tatgtaagtttgcatattcagctacagctagtgcttagaaaacaaatgtgagtggtcaggatctcatgacatttatcttgagt
ttcttcaagatcatttaggatactcttaattcactcattcaatcaaatattttttsagtgtagctgtgagtgaaagag

Fig. 12
Page 29 of 30

tatgtacgtacgtataagactagagagatattaagtctcagtacacttcctgtgccatgttattcagctcactsgtttac
aaatatagggtgtcttgtgggtgtaggagcccaactgtacaataactgggcagccttttttttttttttttaattgcaac
aatgcaaaagccaagaaagttaagggtcacaaagtctaacaatgaattcttcaacagggaaaacagctagcttgaaaac
tgctgaaaaacacaacttgtgtttatggcatttagtaccttcaaatattggcttgcagatattggataccccattaa
atctgacagttcctcaatttttcatctcttcaatcactagtcagaaaaaatataaaaaacaacaataacttccatattggag
catttttcagagttttcctaacccagtcttatttttctagtcagttaaacatttgcataaaatactgtttcactaatacttac
tgtaactgtcttgagagaaaaagaaaaatatgagagaactattgttggggaagtccaagtgatctttcaatatacattac
taacttcttccacttttccagaatttgaatattaacgctaaaggtgtaagacttcagatttcaaatattctttctata
tttttaaatccacagaatattatataaccctgctgaaaaagaaacaaatgattgttttagaagttaaggtcaatat
cgattttcaaatattaag

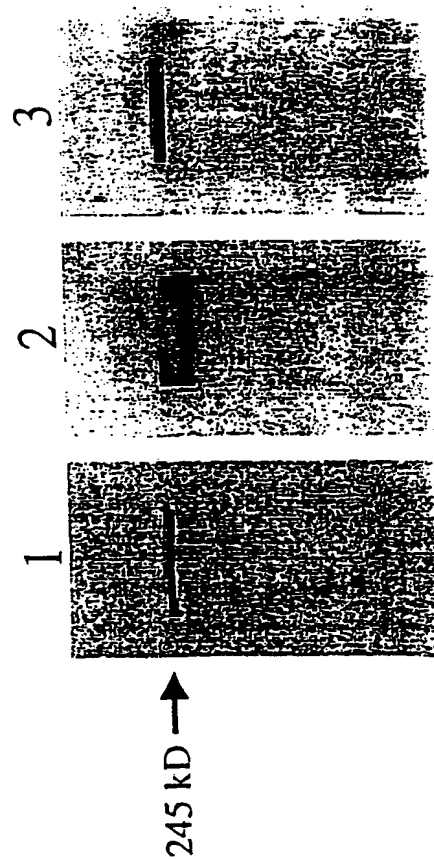


Fig. 13

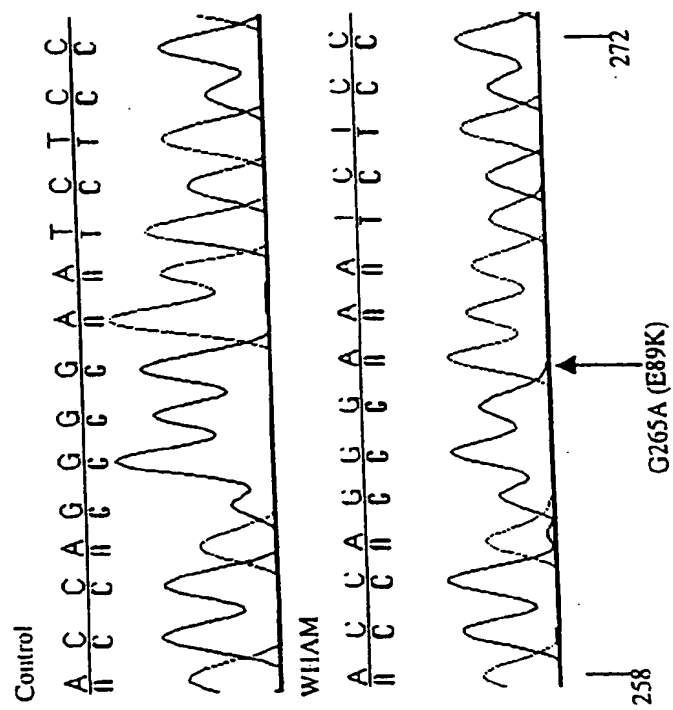


Fig. 14

No.	Name	Location in SEQ ID No. 14	Sequence	Sequence Strand Length
1	PPRE	56-60	AGGTAAAGTCA	12 Complement
2	PPRE	1997-2009	AGAGTAGAGGGCA	13 Lead
3	PPRE	2150-2161	ATGTCAAGTTCA	12 Lead
4	PPRE	2156-2169	AGTTCAAAAGGCA	14 Lead
5	PPRE	4128-4139	AGGCCAGCAGGGCC	14 Complement
6	PPRE	5075-5087	AGGCCAGCAGGTGA	13 Lead
7	PPRE	6604-6615	ATGCCAAAGGTCA	12 Complement
8	PPRE	6731-6743	GGGGCAAAGGTGA	13 Complement
9	PPRE	7220-7233	AGGTAATGAGGACA	14 Complement
10	PPRE	7554-7568	GGATCACGAGGTCA	15 Complement
1	SRE	159-166	CAGCCCAT	8 Lead
2	SRE	1133-1140	CAGCTCAC	8 Complement
3	SRE	1145-1152	CACACCAC	8 Lead
4	SRE	1809-1816	CAGCCCTC	8 Complement
5	SRE	1894-1901	CAGCCCAT	8 Lead
6	SRE	2563-2570	CAACCCAC	8 Lead
7	SRE	3303-3310	CAGCTCAC	8 Lead
8	SRE	3475-3477	CCGCCAC	8 Lead
9	SRE	4784-4791	CTGCCAC	8 Complement
10	SRE	4802-4809	CAGCCTAC	8 Complement
11	SRE	4975-4977	CAGCTCAC	8 Complement
12	SRE	6487-6494	CAGCCTAC	8 Complement
13	SRE	6565-6572	CACCCAAC	8 Complement
14	SRE	6727-6734	CAGCCTAC	8 Lead
15	SRE	7041-7048	CACCCAAC	8 Lead
16	SRE	8059-8066	CAGCCCTC	8 Complement
1	ROR(retinoic acid receptor related)	166-172	AGGGTCA	7 Complement
2	ROR(retinoic acid receptor related)	156-173	AAGGGTCA	8 Complement
3	ROR(retinoic acid receptor related)	263-370	ATGGGTCA	8 Lead
4	ROR(retinoic acid receptor related)	264-370	TGGGTCA	7 Lead
5	ROR(retinoic acid receptor related)	2218-2225	TAGGGTCA	8 Lead
6	ROR(retinoic acid receptor related)	2218-2225	AGGGTCA	7 Lead
7	ROR(retinoic acid receptor related)	3643-3649	TGGGTCA	7 Lead
8	ROR(retinoic acid receptor related)	6654-6660	AAGGTCA	7 Complement
1	SREBP-1 or "E box"	473-479	ACACCTG	7 Complement
2	SREBP-1 or "E box"	536-541	ACACATG	7 Lead
3	SREBP-1 or "E box"	537-543	TCATGTG	7 Complement
4	SREBP-1 or "E box"	666-661	TCATGTG	7 Complement
5	SREBP-1 or "E box"	825-831	ACACTTG	7 Lead
6	SREBP-1 or "E box"	997-873	TCACCTG	7 Lead
7	SREBP-1 or "E box"	968-874	TCAGGTG	7 Complement
8	SREBP-1 or "E box"	1063-1069	ACAGGTG	7 Complement
9	SREBP-1 or "E box"	1124-1110	TCAGGTG	7 Lead
10	SREBP-1 or "E box"	1125-1111	TCAGGTG	7 Complement
11	SREBP-1 or "E box"	1581-1587	TCACCTG	7 Lead
12	SREBP-1 or "E box"	1670-1676	TCAGGTG	7 Lead
13	SREBP-1 or "E box"	1748-1754	ACACTTG	7 Lead
14	SREBP-1 or "E box"	1749-1755	ACAGGTG	7 Complement
15	SREBP-1 or "E box"	1852-1858	TCATGTG	7 Lead
16	SREBP-1 or "E box"	1853-1859	ACACATG	7 Complement
17	SREBP-1 or "E box"	1999-1905	ACAAATG	7 Complement
18	SREBP-1 or "E box"	2199-2205	ACAGGTG	7 Lead
19	SREBP-1 or "E box"	2383-2399	ACAGCTG	7 Complement
20	SREBP-1 or "E box"	2569-27005	ACACCTG	7 Lead
21	SREBP-1 or "E box"	2577-2683	TCACATG	7 Complement
22	SREBP-1 or "E box"	2740-2746	ACAACTG	7 Complement
23	SREBP-1 or "E box"	2969-2975	ACAAATG	7 Lead
24	SREBP-1 or "E box"	2979-2985	ACACATG	7 Lead
25	SREBP-1 or "E box"	2981-2987	ACATGTG	7 Lead
26	SREBP-1 or "E box"	2980-2986	ACATGTG	7 Complement
27	SREBP-1 or "E box"	2982-2988	ACACATG	7 Complement
28	SREBP-1 or "E box"	3461-3467	TCAGGTG	7 Lead
29	SREBP-1 or "E box"	3482-3488	TCACCTG	7 Complement
30	SREBP-1 or "E box"	3547-3553	TCACCTG	7 Complement
31	SREBP-1 or "E box"	3732-3758	ACACATG	7 Lead
32	SREBP-1 or "E box"	4226-4232	TCACCTG	7 Lead
33	SREBP-1 or "E box"	4582-4588	ACAGCTG	7 Complement
34	SREBP-1 or "E box"	4586-4594	TCAGTTG	7 Lead
35	SREBP-1 or "E box"	4861-4867	TCAGGTG	7 Lead
36	SREBP-1 or "E box"	4951-4957	ACAAATG	7 Lead
37	SREBP-1 or "E box"	5096-5102	TCAAATG	7 Complement
38	SREBP-1 or "E box"	5912-5918	ACAGTTG	7 Lead
39	SREBP-1 or "E box"	5913-5919	TCACCTG	7 Complement
40	SREBP-1 or "E box"	6245-6251	ACACATG	7 Complement
41	SREBP-1 or "E box"	6269-6294	ACAACTG	7 Complement
42	SREBP-1 or "E box"	6623-6629	TCATTTG	7 Lead
43	SREBP-1 or "E box"	6836-6842	TCACCTG	7 Lead
44	SREBP-1 or "E box"	6837-6843	ACAGGTG	7 Complement
45	SREBP-1 or "E box"	7032-7038	ACAGGTG	7 Complement

Fig. 16

46 SREBP-1 or "E box"	7069-7075	TCAGGTG	7 Lead
47 SREBP-1 or "E box"	7101-7107	ACATATG	7 Complement
48 SREBP-1 or "E box"	7138-7144	ACAGTTG	7 Lead
49 SREBP-1 or "E box"	7139-7145	TCAACTG	7 Complement
50 SREBP-1 or "E box"	7240-7246	ACACCTG	7 Complement
51 SREBP-1 or "E box"	7467-7473	ACAGGTG	7 Lead
52 SREBP-1 or "E box"	7640-7646	TCATTTG	7 Lead
53 SREBP-1 or "E box"	7641-7647	TCAAATG	7 Complement
54 SREBP-1 or "E box"	7653-7659	TCAGTTG	7 Lead
55 SREBP-1 or "E box"	7654-7660	ACAACTG	7 Complement
56 SREBP-1 or "E box"	7735-7741	ACAAATG	7 Lead
57 SREBP-1 or "E box"	7838-7844	TCAGGTG	7 Complement
58 SREBP-1 or "E box"	7860-7866	TCATCTG	7 Complement
59 SREBP-1 or "E box"	8051-8057	TCAGCTG	7 Lead
60 SREBP-1 or "E box"	8052-8058	TCAGCTG	7 Complement

Fig. 16

SEQUENCE LISTING

<110> University of British Columbia
Xenon Bioresearch, Inc.

<120> METHODS AND REAGENTS FOR MODULATING
CHOLESTEROL LEVELS

<130> 50110/002W05

<150> 60/124,702

<151> 1999-03-15

<150> 60/138,048

<151> 1999-06-08

<150> 60/139,600

<151> 1999-06-17

<150> 60/151,977

<151> 1999-09-01

<160> 287

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 2261

<212> PRT

<213> Homo sapiens

<400> 1

Met	Ala	Cys	Trp	Pro	Gln	Leu	Arg	Leu	Leu	Leu	Trp	Lys	Asn	Leu	Thr
1				5					10					15	
Phe	Arg	Arg	Arg	Gln	Thr	Cys	Gln	Leu	Leu	Glu	Val	Ala	Trp	Pro	
			20					25				30			
Leu	Phe	Ile	Phe	Leu	Ile	Leu	Ile	Ser	Val	Arg	Leu	Ser	Tyr	Pro	Pro
		35				40					45				
Tyr	Glu	Gln	His	Glu	Cys	His	Phe	Pro	Asn	Lys	Ala	Met	Pro	Ser	Ala
	50					55					60				
Gly	Thr	Leu	Pro	Trp	Val	Gln	Gly	Ile	Ile	Cys	Asn	Ala	Asn	Asn	Pro
65					70					75					80
Cys	Phe	Arg	Tyr	Pro	Thr	Pro	Gly	Glu	Ala	Pro	Gly	Val	Val	Gly	Asn
				85					90					95	
Phe	Asn	Lys	Ser	Ile	Val	Ala	Arg	Leu	Phe	Ser	Asp	Ala	Arg	Arg	Leu
			100					105					110		
Leu	Leu	Tyr	Ser	Gln	Lys	Asp	Thr	Ser	Met	Lys	Asp	Met	Arg	Lys	Val
		115					120					125			
Leu	Arg	Thr	Leu	Gln	Gln	Ile	Lys	Lys	Ser	Ser	Ser	Asn	Leu	Lys	Leu
	130					135					140				
Gln	Asp	Phe	Leu	Val	Asp	Asn	Glu	Thr	Phe	Ser	Gly	Phe	Leu	Tyr	His
145					150					155					160
Asn	Leu	Ser	Leu	Pro	Lys	Ser	Thr	Val	Asp	Lys	Met	Leu	Arg	Ala	Asp
				165					170						175

Val Ile Leu His Lys Val Phe Leu Gln Gly Tyr Gln Leu His Leu Thr
 180 185 190
 Ser Leu Cys Asn Gly Ser Lys Ser Glu Glu Met Ile Gln Leu Gly Asp
 195 200 205
 Gln Glu Val Ser Glu Leu Cys Gly Leu Pro Arg Glu Lys Leu Ala Ala
 210 215 220
 Ala Glu Arg Val Leu Arg Ser Asn Met Asp Ile Leu Lys Pro Ile Leu
 225 230 235 240
 Arg Thr Leu Asn Ser Thr Ser Pro Phe Pro Ser Lys Glu Leu Ala Glu
 245 250 255
 Ala Thr Lys Thr Leu Leu His Ser Leu Gly Thr Leu Ala Gln Glu Leu
 260 265 270
 Phe Ser Met Arg Ser Trp Ser Asp Met Arg Gln Glu Val Met Phe Leu
 275 280 285
 Thr Asn Val Asn Ser Ser Ser Ser Thr Gln Ile Tyr Gln Ala Val
 290 295 300
 Ser Arg Ile Val Cys Gly His Pro Glu Gly Gly Glu Lys Ile Lys
 305 310 315 320
 Ser Leu Asn Trp Tyr Glu Asp Asn Asn Tyr Lys Ala Leu Phe Gly Gly
 325 330 335
 Asn Gly Thr Glu Glu Asp Ala Glu Thr Phe Tyr Asp Asn Ser Thr Thr
 340 345 350
 Pro Tyr Cys Asn Asp Leu Met Lys Asn Leu Glu Ser Ser Pro Leu Ser
 355 360 365
 Arg Ile Trp Lys Ala Leu Lys Pro Leu Leu Val Gly Lys Ile Leu
 370 375 380
 Tyr Thr Pro Asp Thr Pro Ala Thr Arg Gln Val Met Ala Glu Val Asn
 385 390 395 400
 Lys Thr Phe Gln Glu Leu Ala Val Phe His Asp Leu Glu Gly Met Trp
 405 410 415
 Glu Glu Leu Ser Pro Lys Ile Trp Thr Phe Met Glu Asn Ser Gln Glu
 420 425 430
 Met Asp Leu Val Arg Met Leu Leu Asp Ser Arg Asp Asn Asp His Phe
 435 440 445
 Trp Glu Gln Gln Leu Asp Gly Leu Asp Trp Thr Ala Gln Asp Ile Val
 450 455 460
 Ala Phe Leu Ala Lys His Pro Glu Asp Val Gln Ser Ser Asn Gly Ser
 465 470 475 480
 Val Tyr Thr Trp Arg Glu Ala Phe Asn Glu Thr Asn Gln Ala Ile Arg
 485 490 495
 Thr Ile Ser Arg Phe Met Glu Cys Val Asn Leu Asn Lys Leu Glu Pro
 500 505 510
 Ile Ala Thr Glu Val Trp Leu Ile Asn Lys Ser Met Glu Leu Leu Asp
 515 520 525
 Glu Arg Lys Phe Trp Ala Gly Ile Val Phe Thr Gly Ile Thr Pro Gly
 530 535 540
 Ser Ile Glu Leu Pro His Val Lys Tyr Lys Ile Arg Met Asp Ile
 545 550 555 560
 Asp Asn Val Glu Arg Thr Asn Lys Ile Lys Asp Gly Tyr Trp Asp Pro
 565 570 575
 Gly Pro Arg Ala Asp Pro Phe Glu Asp Met Arg Tyr Val Trp Gly Gly
 580 585 590
 Phe Ala Tyr Leu Gln Asp Val Val Glu Gln Ala Ile Ile Arg Val Leu
 595 600 605
 Thr Gly Thr Glu Lys Lys Thr Gly Val Tyr Met Gln Gln Met Pro Tyr

610	615	620
Pro Cys Tyr Val Asp Asp Ile Phe Leu Arg Val Met Ser Arg Ser Met		
625	630	635
Pro Leu Phe Met Thr Leu Ala Trp Ile Tyr Ser Val Ala Val Ile Ile		640
	645	650
Lys Gly Ile Val Tyr Glu Lys Glu Ala Arg Leu Lys Glu Thr Met Arg		655
	660	665
Ile Met Gly Leu Asp Asn Ser Ile Leu Trp Phe Ser Trp Phe Ile Ser		670
	675	680
Ser Leu Ile Pro Leu Leu Val Ser Ala Gly Leu Leu Val Val Ile Leu		685
	690	695
Lys Leu Gly Asn Leu Leu Pro Tyr Ser Asp Pro Ser Val Val Phe Val		700
705	710	715
Phe Leu Ser Val Phe Ala Val Val Thr Ile Leu Gln Cys Phe Leu Ile		720
	725	730
Ser Thr Leu Phe Ser Arg Ala Asn Leu Ala Ala Cys Gly Gly Ile		735
	740	745
Ile Tyr Phe Thr Leu Tyr Leu Pro Tyr Val Leu Cys Val Ala p Gln		750
	755	760
Asp Tyr Val Gly Phe Thr Leu Lys Ile Phe Ala Ser Leu Leu Ser Pro		765
770	775	780
Val Ala Phe Gly Phe Gly Cys Glu Tyr Phe Ala Leu Phe Glu Gln Gln		785
785	790	795
Gly Ile Gly Val Gln Trp Asp Asn Leu Phe Glu Ser Pro Val Glu Glu		800
	805	810
Asp Gly Phe Asn Leu Thr Thr Ser Val Ser Met Met Leu Phe Asp Thr		815
	820	825
Phe Leu Tyr Gly Val Met Thr Trp Tyr Ile Glu Ala Val Phe Pro Gly		830
	835	840
Gln Tyr Gly Ile Pro Arg Pro Trp Tyr Phe Pro Cys Thr Lys Ser Tyr		845
850	855	860
Trp Phe Gly Glu Glu Ser Asp Glu Lys Ser His Pro Gly Ser Asn Gln		865
865	870	875
Lys Arg Ile Ser Glu Ile Cys Met Glu Glu Glu Pro Thr His Leu Lys		880
	885	890
Leu Gly Val Ser Ile Gln Asn Leu Val Lys Val Tyr Arg Asp Gly Met		895
	900	905
Lys Val Ala Val Asp Gly Leu Ala Leu Asn Phe Tyr Glu Gly Gln Ile		910
	915	920
Thr Ser Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Met Ser		925
930	935	940
Ile Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Thr Ala Tyr Ile Leu		945
945	950	955
Gly Lys Asp Ile Arg Ser Glu Met Ser Thr Ile Arg Gln Asn Leu Gly		960
	965	970
Val Cys Pro Gln His Asn Val Leu Phe Asp Met Leu Thr Val Glu Glu		975
	980	985
His Ile Trp Phe Tyr Ala Arg Leu Lys Gly Leu Ser Glu Lys His Val		990
	995	1000
Lys Ala Glu Met Glu Gln Met Ala Leu Asp Val Gly Leu Pro Ser Ser		1005
1010	1015	1020
Lys Leu Lys Ser Lys Thr Ser Gln Leu Ser Gly Gly Met Gln Arg Lys		1025
1025	1030	1035
Leu Ser Val Ala Leu Ala Phe Val Gly Gly Ser Lys Val Val Ile Leu		1040
	1045	1050
		1055

Asp Glu Pro Thr Ala Gly Val Asp Pro Tyr Ser Arg Arg Gly Ile Trp
 1060 1065 1070
 Glu Leu Leu Leu Lys Tyr Arg Gln Gly Arg Thr Ile Ile Leu Ser Thr
 1075 1080 1085
 His His Met Asp Glu Ala Asp Val Leu Gly Asp Arg Ile Ala Ile Ile
 1090 1095 1100
 Ser His Gly Lys Leu Cys Cys Val Gly Ser Ser Leu Phe Leu Lys Asn
 1105 1110 1115 1120
 Gln Leu Gly Thr Gly Tyr Tyr Leu Thr Leu Val Lys Lys Asp Val Glu
 1125 1130 1135
 Ser Ser Leu Ser Ser Cys Arg Asn Ser Ser Ser Thr Val Ser Tyr Leu
 1140 1145 1150
 Lys Lys Glu Asp Ser Val Ser Gln Ser Ser Ser Asp Ala Gly Leu Gly
 1155 1160 1165
 Ser Asp His Glu Ser Asp Thr Leu Thr Ile Asp Val Ser Ala Ile Ser
 1170 1175 1180
 Asn Leu Ile Arg Lys His Val Ser Glu Ala Arg Leu Val Glu Asp Ile
 1185 1190 1195 1200
 Gly His Glu Leu Thr Tyr Val Leu Pro Tyr Glu Ala Ala Lys Glu Gly
 1205 1210 1215
 Ala Phe Val Glu Leu Phe His Glu Ile Asp Asp Arg Leu Ser Asp Leu
 1220 1225 1230
 Gly Ile Ser Ser Tyr Gly Ile Ser Glu Thr Thr Leu Glu Glu Ile Phe
 1235 1240 1245
 Leu Lys Val Ala Glu Glu Ser Gly Val Asp Ala Glu Thr Ser Asp Gly
 1250 1255 1260
 Thr Leu Pro Ala Arg Arg Asn Arg Arg Ala Phe Gly Asp Lys Gln Ser
 1265 1270 1275 1280
 Cys Leu Arg Pro Phe Thr Glu Asp Asp Ala Ala Asp Pro Asn Asp Ser
 1285 1290 1295
 Asp Ile Asp Pro Glu Ser Arg Glu Thr Asp Leu Leu Ser Gly Met Asp
 1300 1305 1310
 Gly Lys Gly Ser Tyr Gln Val Lys Gly Trp Lys Leu Thr Gln Gln Gln
 1315 1320 1325
 Phe Val Ala Leu Leu Trp Lys Arg Leu Leu Ile Ala Arg Arg Ser Arg
 1330 1335 1340
 Lys Gly Phe Phe Ala Gln Ile Val Leu Pro Ala Val Phe Val Cys Ile
 1345 1350 1355 1360
 Ala Leu Val Phe Ser Leu Ile Val Pro Pro Phe Gly Lys Tyr Pro Ser
 1365 1370 1375
 Leu Glu Leu Gln Pro Trp Met Tyr Asn Glu Gln Tyr Thr Phe Val Ser
 1380 1385 1390
 Asn Asp Ala Pro Glu Asp Thr Gly Thr Leu Glu Leu Leu Asn Ala Leu
 1395 1400 1405
 Thr Lys Asp Pro Gly Phe Gly Thr Arg Cys Met Glu Gly Asn Pro Ile
 1410 1415 1420
 Pro Asp Thr Pro Cys Gln Ala Gly Glu Glu Glu Trp Thr Thr Ala Pro
 1425 1430 1435 1440
 Val Pro Gln Thr Ile Met Asp Leu Phe Gln Asn Gly Asn Trp Thr Met
 1445 1450 1455
 Gln Asn Pro Ser Pro Ala Cys Gln Cys Ser Ser Asp Lys Ile Lys Lys
 1460 1465 1470
 Met Leu Pro Val Cys Pro Pro Gly Ala Gly Gly Leu Pro Pro Pro Gln
 1475 1480 1485
 Arg Lys Gln Asn Thr Ala Asp Ile Leu Gln Asp Leu Thr Gly Arg Asn

1490	1495	1500
Ile Ser Asp Tyr Leu Val Lys Thr Tyr Val Gln Ile Ile Ala Lys Ser		
1505	1510	1515
Leu Lys Asn Lys Ile Trp Val Asn Glu Phe Arg Tyr Gly Gly Phe Ser		1520
	1525	1530
Leu Gly Val Ser Asn Thr Gln Ala Leu Pro Pro Ser Gln Glu Val Asn		1535
	1540	1545
Asp Ala Ile Lys Gln Met Lys Lys His Leu Lys Leu Ala Lys Asp Ser		1550
	1555	1560
Ser Ala Asp Arg Phe Leu Asn Ser Leu Gly Arg Phe Met Thr Gly Leu		1565
	1570	1575
Asp Thr Arg Asn Asn Val Lys Val Trp Phe Asn Asn Lys Gly Trp His		1580
1585	1590	1595
Ala Ile Ser Ser Phe Leu Asn Val Ile Asn Asn Ala Ile Leu Arg Ala		1600
	1605	1610
Asn Leu Gln Lys Gly Glu Asn Pro Ser His Tyr Gly Ile Thr Ala Phe		1615
	1620	1625
Asn His Pro Leu Asn Leu Thr Lys Gln Gln Leu Ser Glu Val Ala Leu		1630
	1635	1640
Met Thr Thr Ser Val Asp Val Leu Val Ser Ile Cys Val Ile Phe Ala		1645
	1650	1655
Met Ser Phe Val Pro Ala Ser Phe Val Val Phe Leu Ile Gln Glu Arg		1660
1665	1670	1675
Val Ser Lys Ala Lys His Leu Gln Phe Ile Ser Gly Val Lys Pro Val		1680
	1685	1690
Ile Tyr Trp Leu Ser Asn Phe Val Trp Asp Met Cys Asn Tyr Val Val		1695
	1700	1705
Pro Ala Thr Leu Val Ile Ile Ile Phe Ile Cys Phe Gln Gln Lys Ser		1710
	1715	1720
Tyr Val Ser Ser Thr Asn Leu Pro Val Leu Ala Leu Leu Leu Leu		1725
	1730	1735
Tyr Gly Trp Ser Ile Thr Pro Leu Met Tyr Pro Ala Ser Phe Val Phe		1740
1745	1750	1755
Lys Ile Pro Ser Thr Ala Tyr Val Val Leu Thr Ser Val Asn Leu Phe		1760
	1765	1770
Ile Gly Ile Asn Gly Ser Val Ala Thr Phe Val Leu Glu Leu Phe Thr		1775
	1780	1785
Asp Asn Lys Leu Asn Asn Ile Asn Asp Ile Leu Lys Ser Val Phe Leu		1790
	1795	1800
Ile Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Met Val Lys		1805
	1810	1815
Asn Gln Ala Met Ala Asp Ala Leu Glu Arg Phe Gly Glu Asn Arg Phe		1820
1825	1830	1835
Val Ser Pro Leu Ser Trp Asp Leu Val Gly Arg Asn Leu Phe Ala Met		1840
	1845	1850
Ala Val Glu Gly Val Val Phe Phe Leu Ile Thr Val Leu Ile Gln Tyr		1855
	1860	1865
Arg Phe Phe Ile Arg Pro Arg Pro Val Asn Ala Lys Leu Ser Pro Leu		1870
	1875	1880
Asn Asp Glu Asp Glu Asp Val Arg Arg Glu Arg Gln Arg Ile Leu Asp		1885
	1890	1895
Gly Gly Gly Gln Asn Asp Ile Leu Glu Ile Lys Glu Leu Thr Lys Ile		1900
1905	1910	1915
Tyr Arg Arg Lys Arg Lys Pro Ala Val Asp Arg Ile Cys Val Gly Ile		1920
	1925	1930
		1935

Pro Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys
 1940 1945 1950
 Ser Ser Thr Phe Lys Met Leu Thr Gly Asp Thr Thr Val Thr Arg Gly
 1955 1960 1965
 Asp Ala Phe Leu Asn Lys Asn Ser Ile Leu Ser Asn Ile His Glu Val
 1970 1975 1980
 His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Thr Glu Leu
 1985 1990 1995 2000
 Leu Thr Gly Arg Glu His Val Glu Phe Phe Ala Leu Leu Arg Gly Val
 2005 2010 2015
 Pro Glu Lys Glu Val Gly Lys Val Gly Glu Trp Ala Ile Arg Lys Leu
 2020 2025 2030
 Gly Leu Val Lys Tyr Gly Glu Lys Tyr Ala Gly Asn Tyr Ser Gly Gly
 2035 2040 2045
 Asn Lys Arg Lys Leu Ser Thr Ala Met Ala Leu Ile Gly Gly Pro Pro
 2050 2055 2060
 Val Val Phe Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg
 2065 2070 2075 2080
 Arg Phe Leu Trp Asn Cys Ala Leu Ser Val Val Lys Glu Gly Arg Ser
 2085 2090 2095
 Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr
 2100 2105 2110
 Arg Met Ala Ile Met Val Asn Gly Arg Phe Arg Cys Leu Gly Ser Val
 2115 2120 2125
 Gln His Leu Lys Asn Arg Phe Gly Asp Gly Tyr Thr Ile Val Val Arg
 2130 2135 2140
 Ile Ala Gly Ser Asn Pro Asp Leu Lys Pro Val Gln Asp Phe Phe Gly
 2145 2150 2155 2160
 Leu Ala Phe Pro Gly Ser Val Leu Lys Glu Lys His Arg Asn Met Leu
 2165 2170 2175
 Gln Tyr Gln Leu Pro Ser Ser Leu Ser Ser Leu Ala Arg Ile Phe Ser
 2180 2185 2190
 Ile Leu Ser Gln Ser Lys Lys Arg Leu His Ile Glu Asp Tyr Ser Val
 2195 2200 2205
 Ser Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Asp Gln
 2210 2215 2220
 Ser Asp Asp Asp His Leu Lys Asp Leu Ser Leu His Lys Asn Gln Thr
 2225 2230 2235 2240
 Val Val Asp Val Ala Val Leu Thr Ser Phe Leu Gln Asp Glu Lys Val
 2245 2250 2255
 Lys Glu Ser Tyr Val
 2260

<210> 2

<211> 7864

<212> DNA

<213> Homo sapiens

<400> 2

gtccctgctg	tgagctctgg	ccgctgcctt	ccagggctcc	cgagccacac	gctgggggtg	60
ctggctgagg	gaacatggct	tggtggcctc	agctgaggtt	gctgctgtgg	aagaacctca	120
ctttcagaag	aagacaaaca	tgtcagctgt	tactggaagt	ggcctggcct	ctatttatct	180
tcttgatcct	gatctctgtt	cggctgagct	accacccta	tgaacaacat	gaatgccatt	240
ttccaaataa	agccatgccc	tctgcaggaa	cacttccttg	ggttcagggg	attatctgta	300
atgccaaaca	cccctgtttc	cgttaccoga	ctcctgggga	ggctcccggg	gttggttgaa	360

actttaacaa	atccattgtg	gctcgccctgt	tctcagatgc	tccgaggcctt	cttttataca	420
gccagaaaga	caccagcatg	aaggacatgc	gcaaagttct	gagaacatta	cagcagatca	480
agaaatccag	ctcaaacttg	aagcttcaag	atttctctgg	ggacaatgaa	accttctctg	540
ggttcctgta	tcacaacctc	tctctcccaa	agtctactgt	ggacaagatg	ctgagggctg	600
atgtcattct	ccacaaggta	tttttgcaag	gctaccagtt	acatttgaca	agtctgtgca	660
atggatcaaa	atcagaagag	atgattcaac	ttggtgacca	agaagtttct	gagctttgtg	720
gcctaccaag	ggagaaactg	gctgcagcag	agcgagtact	tcgttccaac	atggacatcc	780
tgaagccaat	cctgagaaca	ctaaactcta	catctccctt	cccagcaag	gagctggctg	840
aagccacaaa	aacattgctg	catagtcttg	ggactctggc	ccaggagctg	ttcagcatga	900
gaagctggag	tgacatgcga	caggaggtga	tgtttctgac	caatgtgaac	agctccagct	960
cctccaccca	aatctaccag	gctgtgtctc	gtattgtctg	cgggcatccc	gagggagggg	1020
ggctgaagat	caagtctctc	aactgggtatg	aggacaacaa	ctacaaagcc	ctctttggag	1080
gcaatggcac	tgaggaagat	gctgaaacct	tctatgacaa	ctctacaact	ccttactgca	1140
atgatttgat	gaagaatttg	gagtgtagtc	ctctttcccg	cattatctgg	aaagctctga	1200
agccgctgct	cgttgggaag	atcctgtata	cacctgacac	tccagccaca	aggcaggtca	1260
tggctgaggt	gaacaagacc	ttccaggaac	tggctgtgtt	ccatgatctg	gaaggcatgt	1320
gggaggaact	cagccccaag	atctggacct	tcattggagaa	cagccaagaa	atggaccttg	1380
tccggatgct	gttggaacag	agggacaatg	accacttttg	ggaacagcag	ttggatggct	1440
tagattggac	agcccaagac	atcgtggcgt	ttttggccaa	gcaccagag	gatgtccagt	1500
ccagtaatgg	ttctgtgtac	acctggagag	aagctttcaa	cgagactaac	caggcaatcc	1560
ggaccatata	tcgcttcatg	gagtggtgca	acctgaacaa	gctagaaccc	atagcaacag	1620
aagtctggct	catcaacaag	tccatggagc	tgctggatga	gaggaagttc	tgggctggta	1680
ttgtgttcac	tgggaattact	ccaggcagca	ttgagctgcc	ccatcatgtc	aagtacaaga	1740
tccgaatgga	cattgacaat	gtggagagga	caaataaaaat	caaggatggg	tactgggacc	1800
ctggtcctcg	agctgacccc	tttgaggaca	tgcggtagct	ctgggggggg	ttcgccact	1860
tgcaggatgt	ggtggagcag	gcaatcatca	gggtgctgac	gggcaccgag	aagaaaactg	1920
gdgtgtctat	atgcaacaga	tgccctatcc	ctgttacgtt	gatgacatct	ttctgcgggt	1980
gatgagccgg	tcaatgcccc	tcttcagcac	gctggcctgg	atttactcag	tggctgtgat	2040
catcaagggc	atcgtgtatg	agaaggaggc	acggctgaaa	gagaccatgc	ggatcatggg	2100
cctggacaac	agcatcctct	ggtttagctg	gttcattagt	agcctcattc	ctcttcttgt	2160
gagcgctggc	ctgctagtgg	tcatectgaa	gttaggaaac	ctgctgccct	acagtgatcc	2220
cagcggtggt	tttgtcttcc	tgtccgtgtt	tgctgtgggt	acaatcctgc	agtgttctct	2280
gattagcaca	ctcttctcca	gagccaacct	ggcagcagcc	tgtgggggca	tcactacttt	2340
cacgctgtac	ctgccctacg	tctgtgtgtg	ggcatggcag	gactacgtgg	gcttcacact	2400
caagatcttc	gctagcctgc	tgtctcctgt	ggcttttggt	tttggctgtg	agtactttgc	2460
cctttttgag	gagcagggca	ttggagtgcg	gtgggacaac	ctggttgaga	gtcctgtgga	2520
ggaagatggc	ttcaatctca	ccacttcggt	ctccatgatg	ctggttgaca	ccttctctta	2580
tggggtgatg	acctggtaga	ttgaggctgt	ctttccaggc	cagtacggaa	ttcccaggcc	2640
ctggtatatt	ccttgcacca	agtcctactg	gtttggcgag	gaaagtgatg	agaagagcca	2700
ccctggttcc	aaccagaaga	gaatatcaga	aatctgcatg	gaggaggaac	ccacccactt	2760
gaagctgggc	gtgtccattc	agaacctggt	aaaagtctac	cgagatggga	tgaagggtgg	2820
tgtcgatggc	ctggcactga	atttttatga	gggccagatc	acctccttcc	tgggccacaa	2880
tggagcgggg	aagacgacca	ccatgtcaat	cctgacgggg	ttgttcccc	cgacctcggg	2940
caccgcctac	atcctgggaa	aagacattcg	ctctgagatg	agcaccatcc	ggcagaacct	3000
gggggtctgt	ccccagcata	acgtgctgtt	tgacatgctg	actgtcgaag	aacacatctg	3060
gttctatgcc	cgcttgaaag	ggctctctga	gaagcacgtg	aaggcggaga	tggagcagat	3120
ggccctggat	gttggtttgc	catcaagcaa	gctgaaaagc	aaaacaagcc	agctgtcagg	3180
tggaatgcag	agaaagctat	ctgtggcctt	ggcctttgtc	gggggatcta	aggttgtcat	3240
tctggatgaa	cccacagctg	gtgtggaccc	ttactcccg	aggggaatat	gggagctgct	3300
gctgaaatcc	cgacaaggcc	gcaccattat	tctctctaca	caccacatgg	atgaagcgga	3360
cgtcctgggg	gacaggattg	ccatcatctc	ccattgggaag	ctgtgctgtg	tgggctctct	3420
cctgtttctg	aagaaccagc	tgggaacagg	ctactacctg	accttgggtc	agaaagatgt	3480
ggaatcctcc	ctcagttcct	gcagaaacag	tagtagcact	gtgtcatacc	tgaaaaagga	3540
ggacagtgtt	tctcagagca	gttctgatgc	tggcctgggg	agcgaccatg	agagtgcac	3600
gctgaccatc	gatgtctctg	ctatctccaa	cctcatcagg	aagcatgtgt	ctgaagcccg	3660

gctgggtggaa	gacatagggc	atgagctgac	ctatgtgctg	ccatatgaag	ctgctaagga	3720
gggagccttt	gtggaactct	ttcatgagat	tgatgaccgg	ctctcagacc	tgggcatttc	3780
tagttatggc	atctcagaga	cgacctgga	agaaatattc	ctcaaggtgg	ccgaagagag	3840
tgggggtggat	gctgagacct	cagatggtag	cttgccagca	agacgaaaca	ggcggggcctt	3900
cggggacaag	cagagctgtc	ttcgcccggt	caactgaagat	gatgctgctg	atccaaatga	3960
ttgctgacat	agaccagaa	tccagagaga	cagacttgct	cagtgggatg	gatggcaaag	4020
ggctctacca	ggtgaaaggc	tggaaactta	cacagcaaca	gtttgtggcc	ctttgtgga	4080
agagactgct	aattgccaga	cggagtggga	aaggattttt	tgctcagatt	gtcttgccag	4140
ctgtgtttgt	ctgcattgcc	cttgtgttca	gcctgatcgt	gccacctttt	ggcaagtacc	4200
ccagcctgga	acttcagccc	tggatgtaca	acgaacagta	cacatttgct	agcaatgatg	4260
ctcctgagga	cacgggaacc	ctggaactct	taaagccctt	caccaaagac	cctggcttcg	4320
ggacctcgctg	tatggaagga	aacccaatcc	cagacacgcc	ctgccaggca	ggggaggaag	4380
agtggaccac	tgccccagtt	ccccagacca	tcattggacct	cttcagaaat	gggaactgga	4440
caatgcagaa	cccttcacct	gcattgccagt	gtagcagcga	caaaatcaag	aagatgctgc	4500
ctgtgtgtcc	cccaggggca	ggggggctgc	ctcctccaca	aagaaaacaa	aacactgcag	4560
atctccttca	ggacctgaca	ggaagaaaca	tttcggatta	tctgggtgaag	acgtatgtgc	4620
agatcatagc	caaaagctta	aagaacaaga	tctgggtgaa	tgagttagg	tatggcggct	4680
tttccctggg	tgtcagtaat	actcaagcac	ttcctccgag	tcaagaagtt	aatgatgcca	4740
tcaaacaat	gaagaaacac	ctaaagctgg	ccaaggacag	ttctgcagat	cgatttctca	4800
acagcttggg	aagatttatg	acaggactgg	acaccagaaa	taatgtcaag	gtgtggttca	4860
ataacaaggg	ctggcatgca	atcagctctt	tcctgaatgt	catcaacaat	gccattctcc	4920
gggccaacct	gcaaaaggga	gagaacccta	gccattatgg	aattactgct	ttcaatcatc	4980
ccctgaatct	caccaagcag	cagctctcag	aggtggctct	gatgaccaca	tcagtggatg	5040
tccttgtgtc	catctgtgtc	atctttgcaa	tgtccttcgt	cccagccagc	tttgtcgtat	5100
tcctgatcca	ggagcgggtc	agcaaagcaa	aacacctgca	gttcatcagt	ggagtgaagc	5160
ctgtcatcta	ctggctctct	aattttgtct	gggatatgtg	caattacgtt	gtccctgcca	5220
cactggtcat	tatcatcttc	atctgcttcc	agcagaagtc	ctatgtgtcc	tccaccaate	5280
tgcctgtgct	agcccttcta	cttttgctgt	atgggtggtc	aatcacacct	ctcatgtacc	5340
cagcctcctt	tgtgttcaag	atccccagca	cagcctatgt	gggtgctcacc	agcgtgaacc	5400
tcttcatttg	cattaatggc	agcgtggcca	cctttgtgct	ggagctgttc	accgacaata	5460
agctgaataa	tatcaatgat	atcctgaagt	ccgtgttctt	gatcttccca	catttttgcc	5520
tgggacgagg	gctcatcgac	atgggtgaaa	accaggcaat	ggctgatgcc	ctggaaaggt	5580
ttggggagaa	tcgctttgtg	tcaccattat	cttgggactt	ggtgggacga	aacctcttcg	5640
ccatggccgt	ggaaggggtg	gtgttcttcc	tcattactgt	tctgatccag	tacagattct	5700
tcattcagggc	cagacctgta	aatgcaaagc	tatctcctct	gaatgatgaa	gatgaagatg	5760
tgaggcggga	aagacagaga	attcttgatg	gtggaggcca	gaatgacatc	ttagaaatca	5820
aggagttagc	gaagatatat	agaaggaagc	ggaagcctgc	tgtagacagg	atttgctgtg	5880
gcattcctcc	tgttgagtgc	tttgggctcc	tgggagttaa	tggggctgga	aaatcatcaa	5940
ctttcaagat	gttaacagga	gataccactg	ttaccagagg	agatgctttc	cttaacaaaa	6000
ataggtatct	tatcaaaccat	ccatgaagta	catcagaaca	tgggctactg	ccctcagttt	6060
gatgccatca	cagagctgtt	gactgggaga	gaacacgtgg	agttctttgc	ccttttgaga	6120
ggagtcccag	agaaagaagt	tggcaagggt	ggtgagtggg	cgattcggaa	actgggcctc	6180
gtgaagtatg	gagaaaaata	tgctggtaac	tatagtggag	gcaacaaacg	caagctctct	6240
acagccatgg	ctttgatcgg	cgggcctcct	gtgggtgttc	tggatgaacc	caccacaggc	6300
atggatccca	aagcccggtg	gttcttgtgg	aattgtgccc	taagtgttgt	caaggagggg	6360
agatcagtag	tgettacatc	tcattagtatg	gaagaatgtg	aagctctttg	cactaggatg	6420
gcaatcatgg	tcaatggaag	gttcagggtgc	cttggcagtg	tccagcatct	aaaaaataag	6480
tttgagatg	gttatacaat	agttgtacga	atagcagggt	ccaacccgga	cctgaagcct	6540
gtccaggatt	tctttggact	tgcatcttct	ggaagtgttc	taaaagagaa	acaccggaac	6600
atgctacaat	accagcttcc	atcttcatta	tcttctctgg	ccaggatatt	cagcatcctc	6660
tcccagagca	aaaagcgact	ccacatagaa	gactactctg	tttctcagac	aacacttgac	6720
caagtatttg	tgaactttgc	caaggaccaa	agtactgatg	accacttaaa	agacctctca	6780
ttacacaaaa	accagacagt	agtggacgtt	gcagtcttca	catcttttct	acaggatgag	6840
aaagtgaag	aaagctatgt	atgaagaatc	ctgttcatatc	gggggtggctg	aaagtaaaaga	6900
ggaactagac	tttcccttgc	accatgtgaa	gtgttgtgga	gaaaagagcc	agaagttgat	6960

gtgggaagaa	gtaaactgga	tactgtactg	atactattca	atgcaatgca	attcaatgca	7020
atgaaaacaa	aattccatta	caggggcagt	gcctttgtag	cctatgtctt	gtatggctct	7080
caagtgaag	acttgaattt	agttttttac	ctatacctat	gtgaaactct	attatggaac	7140
ccaatggaca	tatgggtttg	aactcacact	tttttttttt	tttttgttcc	tgtgtattct	7200
cattgggggt	gcaacaataa	ttcatcaagt	aatcatggcc	agcgattatt	gatcaaaaatc	7260
aaaaggtaat	gcacatcctc	attcactaag	ccatgccatg	cccaggagac	tggtttcccg	7320
gtgacacatc	cattgctggc	aatgagtgtg	ccagagttat	tagtgccaag	tttttcagaa	7380
agtttgaagc	accatgggtg	gtcatgctca	cttttgtgaa	agctgctctg	ctcagagtct	7440
atcaacattg	aatatcagtt	gacagaatgg	tgccatgcgt	ggctaacatc	ctgctttgat	7500
tccctctgat	aagctgttct	ggtggcagta	acatgcaaca	aaaatgtggg	tgtctccagg	7560
cacgggaaac	ttggttccat	tgttatatgt	tcctatgctt	cgagccatgg	gtctacaggg	7620
tcctccttat	gagactctta	aatatactta	gaccttggtg	agaggcaaag	aatcaacagc	7680
caaactgctg	gggctgcaac	tgctgaagcc	agggcatggg	attaaagaga	ttgtgcgttc	7740
aaacctaggg	aagcctgtgc	ccatttgtcc	tgactgtctg	ctaacatggt	acactgcatc	7800
tcaagatgtt	tatctgacac	aagtgtatta	tttctggctt	tttgaattaa	tctagaaaat	7860
gaaa						7864

<210> 3
 <211> 22
 <212> DNA
 <213> Homo sapiens

<400> 3
 gcagagggca tggctttatt tg 22

<210> 4
 <211> 24
 <212> DNA
 <213> Homo sapiens

<400> 4
 ctgccaggca ggggaggaag agtg 24

<210> 5
 <211> 23
 <212> DNA
 <213> Homo sapiens

<400> 5
 gaaagtgact cacttgtgga gga 23

<210> 6
 <211> 20
 <212> DNA
 <213> Homo sapiens

<400> 6
 aaaggggctt ggtaagggtg 20

<210> 7
 <211> 20
 <212> DNA
 <213> Homo sapiens

<400> 7
catgcacatg cacacacata 20

<210> 8
<211> 27
<212> DNA
<213> Homo sapiens

<400> 8
ctttctgcgg gtgatgagcc ggtcaat 27

<210> 9
<211> 20
<212> DNA
<213> Homo sapiens

<400> 9
ccttagcccg tggtgagcta 20

<210> 10
<211> 26
<212> DNA
<213> Homo sapiens

<400> 10
cctgtaaagc caaagctatc tcctct 26

<210> 11
<211> 26
<212> DNA
<213> Homo sapiens

<400> 11
cgtcaactcc ttgatttcta agatgt 26

<210> 12
<211> 20
<212> DNA
<213> Homo sapiens

<400> 12
gggttcccag gggttcagtat 20

<210> 13
<211> 21
<212> DNA
<213> Homo sapiens

<400> 13
gatcaggaat tcaagcacca a 21

<210> 14
<211> 10545
<212> DNA
<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(10545)

<223> n = a, t, c, or g

<400> 14

acctcttata	gaatgataga	attcctcttg	aatgattgga	taacttcatt	tcctccttga	60
cttttacctt	ggaggatttc	ttaccccttt	tggcttctca	aatttgacta	ttaaaatgtt	120
gcctttaaaa	ataggaacac	agtttcaggg	gggagtacca	gcccagacc	cttctgcaag	180
gccccctaac	tcaaggtagt	ttccctggaa	ctgtggttta	tggaaatgtt	caggagtgtg	240
aggagggtata	atttaaggct	gtcctagcaa	ggataccctt	aaggatagag	ggcccagtag	300
catctggagg	ccagaaaagt	taaactgagg	cagtcagatt	agcttcaggc	tcaattaagc	360
tgatgggtca	gcctgggaga	aattgcagga	tgactctcaa	tatccctcc	cacccccaca	420
gcagccacga	tctgtctgtc	tttaaatcatg	ggtgcagtga	acctgttctt	tccagggtgtc	480
ttggccttca	gtaaccttgt	taggcttgtc	cctgaacgtg	gctaccgatc	caaagacaca	540
tgatcagaga	ggcaattaga	gaacagacct	tttccaaagc	aagcatgttc	tgttgggctt	600
agaagtttca	gttcctaata	ttataggacc	ctgtgcattc	ctctggagat	gaggcacatg	660
agtcatatct	gtgattcttg	cttttgtgtc	aacatctcat	gaataggcaa	tcagagcttt	720
ggcaccaatg	tattttcagt	tcatatctga	tgtagttaaa	tccacctcct	gctttgtagt	780
ttactggcaa	gctgtttttg	atataagaca	tctagaacac	tgtaaataata	taacattttt	840
atgtgtctat	tatacctcaa	ttacgaaaaa	gacatctaga	agcaacctca	tcaagagaga	900
tactgaggcc	gggcatggta	gctcacactt	gcaatcccat	tactttggga	ggctgaggca	960
ggtagatcac	ttgagggtcaa	gagtttgaaa	ccagcctggc	caacatgttg	aaacctgtc	1020
tctattaaaa	atacaaaaaa	gttagctggg	cttggtggtg	ggcacctgta	atcccagcta	1080
ctccggaggc	tgaggcagga	gaatcaactg	aacctgggag	gcagagggtg	cagtgtgctg	1140
agatcacacc	atgcactcc	aacctgggca	ccagagttag	attacatcta	aaaaataaaa	1200
taaagtaata	aaaaagagag	atattgtatg	ctgttgttgg	aaatttcaac	ttccatctca	1260
cttctggtaa	ctttttggaa	gtttgttgaa	caaagtggaa	tacacgcaca	tacacacaca	1320
cacatactct	cttgttttgt	taagggtttaa	tgaaatagct	gtcatataat	cactgttttt	1380
gaaagaggag	aattagttgc	tatctgtaca	ttttgggtat	gtgaactatt	tggatagaac	1440
tctgagaaat	gcattcagaa	caacaaacaa	aatcatagga	gaaatagcta	agtgggaagg	1500
ggcatataag	agttgttgaa	aaagttattt	cttgagaaac	cagctctaata	gctaggcaag	1560
tcacttgctt	tgggggaggc	ctcagcttct	ctgtctataa	gattgcagca	ggggtgtagt	1620
gggaatgagt	cttcaacatt	ccaagagatt	ttatctacta	atacgacagt	caaattggagc	1680
atgactttgt	ggaagcctct	cctcttccac	ccagaggggc	caatttctct	gtcccagtga	1740
gatgttgaca	cttgtatgat	ccctgcttgg	agacttccct	cttctggaac	ctgccctggc	1800
tcaggcatga	gggtgactg	tcaccttctg	ataggagccc	agcactaaag	ctcatgtgtt	1860
ggcagtgttc	ttgcgggaag	gaaaaagacc	agccagccca	tttgttactg	cacaagcaaa	1920
cagcttcttg	tagctgtaca	gatacatgca	ctttctttcc	tcactgtgtt	tccatagaca	1980
gatttagtgc	tgtagaagag	tagagggcag	tcacgggaag	gagttcctgt	ttttcttttg	2040
gctatgccaa	atggggaaaa	atcctcctat	cttgtctttt	tagtgtcatc	ctctctcccc	2100
ttttcttctt	ctttataatt	ctcatctctc	atctctcctg	gaaatgtgca	tgtcaagttc	2160
aaaagggcac	aatgtttttg	tgaggaagag	gtgggagaac	acgtgccagg	tgctaactag	2220
ggtcatcatt	tcccccttca	cagccagctt	cctgtgaatg	tgtgtgtgtg	tgtgtgtgtg	2280
tgtgtgtgtg	tgtgtgtgtg	tgtgtatttc	ttttgccagc	atcactgaat	ctgtctgctg	2340
tctggtatcc	cagggttttg	tttagggaaa	agtaaaagta	atttttataat	cccagctgtc	2400
atttaagcca	cccttttgtg	ggtagcatat	ggtccactct	ctcagttcat	tgtcctaaag	2460
atgcttcatt	agaaaggaat	aacttccacc	ccgttactct	ctgtccccct	actctgcttt	2520
atttttcttc	gtcaatccta	ccaccaccac	ccactgtttg	aacaaccac	tattatttgt	2580
ctgtttccca	tccctggtag	aataggagcc	ccatgaatga	aggaactttg	cttctgttgt	2640
tcaccactga	atctctaagg	tatggaacac	acctggcatg	tgataggcac	tcgataaata	2700
tttggtgtgg	ctcatgggca	ccttgcagag	ttaaggctgc	agttgtttgt	ggaatttata	2760
agtggtaatg	aatatattatc	tactattcct	cttccaaggc	gatcacacaa	taatcaggct	2820
ttacactatc	cagttcttag	gtcttccaag	ttatgacttg	tgaggtagtg	taattatgat	2880
aatagaaggc	agtttatattg	gttcagattt	attgatgtgt	aatttaccac	agtaagactt	2940

ccccctttaca	aaagtatgat	gagttttgac	aaatggatac	acatgtgtat	ctaccactgc	3000
catgctcctt	ttcagtcctgt	cgtccccctcc	acccatgacc	actggtcacc	actgcagtgga	3060
tttctgtccc	cttcatttca	ccttttccag	aatgtcatat	aaatggaatc	atgcagtatg	3120
tagttttttg	tgtctggctt	atttttctta	gcattaggct	tttgggattc	atccagggtg	3180
tcgcatgtaa	cagtagctta	ttccttttta	tggctgagta	agtgtcccag	ttttatttat	3240
atattttattt	atgaggaggt	gtctcactct	gtcaccagag	ctggagtgcg	gtagcgcgat	3300
ctcagctcac	tgcaacctcc	gcctcccagg	ttcaagcaat	tctcctgcct	cctgagtgcg	3360
tgggattaca	ggcaccacc	gccacgccc	actaattttt	atatttttag	tagagatggg	3420
gtttcaccat	gttggccagg	ctgatctcaa	actcttgacc	tcagggtgatc	cgccacctc	3480
tggctcccaa	agtgttagga	ttacaggcat	gagccactgt	gcccagcccc	agttttattt	3540
attcaccagt	tgatggtctt	ttcgacaact	aattgtttcc	agtttttggc	tattctgtat	3600
aaggcttcta	taaatattca	caaataccta	ggatgggatg	actgggtcat	ataatagtac	3660
tgtataacct	tagcagaaac	tgtcaaacta	ttttccaaag	tggctcttcc	attttacaat	3720
tccacagtgt	attgagtccc	agtgtctcca	tacacatgct	agcactttta	atatttaatt	3780
tagtgggtat	gtaatgat	ctcattgtgg	ttttaatttg	catttctctg	cagctaataa	3840
tgagtgtttc	tgcttatttg	ggaagggttt	aatttagcag	tctgttgat	tctgtagata	3900
ttaataactt	caaaatatca	gtggcatttg	cagttaaaa	ttccttaaaa	aattggccaa	3960
agggtttccag	cagtcacttc	tgccatgccc	aaactgtatg	aaacaaggct	gagggtgtgga	4020
gattgtcaca	ttttggcaag	gagtgatcca	cttgggtgac	tgatgagacc	cagagagcgt	4080
acgcctcggg	cttgagggtg	aggacgggctg	ggaagtgcac	tgcatggccc	tgctggcctt	4140
gggaggctgc	ccagtcctta	gctaaagctg	gcagttatgg	gaaacagact	tagattctat	4200
tacgtttttc	aggatgtccc	aggagtcacc	tgggaagctc	agcagtcctt	tgtgactttc	4260
aagcatatgg	tagaagctgc	tgaacacaga	gctccctctt	tggggataat	ttgccccaat	4320
cattttaatca	ggcttgagaa	atgagttacc	acagggtccag	gagtgtctgc	acccttgaat	4380
tctgacaccc	tatttctcct	atccgtctct	taattaatta	agcagacatc	cccaagtgtt	4440
tacgacaagc	caggaccctt	ttgcatacta	aggaaaacag	ggatgaagga	aacagaaatg	4500
gtctctgctc	tgactcagaa	ggtagaaatc	ctctttccca	gccaagtctt	cctagggagc	4560
acgtaggaag	ggctctgaac	ccacgtgtca	gttgcagggg	aggatatcag	gaaaggacat	4620
tgaagaagtg	gagacctaa	tttgagacct	aggcattatg	caggctagca	gtgcttgaaa	4680
aagtgtctta	ggacaagaga	actcaccagt	gaagtcccag	tggtaggaga	gcgtgcagca	4740
tattctgagc	ctgtatacac	atctccaggg	cattgtcttag	cagggtggga	gtggcaagag	4800
agtaggctgg	agtcacagaa	gggaggccag	gtagaccttg	gtgagcactg	gactctatgt	4860
tcagggtgctg	aggagctggc	aaaagggttt	aagtcgggga	gaggcatgtt	cagatatttg	4920
gtctagctga	gtaactttgg	gtgctctgtg	acaaatgggt	gggagaccag	tgagggtggca	4980
gttgcggtca	tctaggagca	ggatcagagt	ggcctattga	ctgggatgac	tgtgaagtgg	5040
gatcctttcc	agccagtaac	tggaaatgtg	tatgagggca	gaagtgaagt	tactgcattt	5100
gaaacattga	gaaatctagt	acatagtact	gtctctttta	tatctttttt	tttttttttt	5160
ttgatttttg	tttgtttgtt	cactaacttg	gaaaactgat	gtggaaatgt	ccctttggct	5220
tcagttacct	gagcagaagg	ggccgggcat	tgccaaactc	tcctcttagg	acagaattgc	5280
tcccagttat	gatcattgtg	ttctgagttg	ggggagcaaa	ttgtgcagga	ggccagggtca	5340
gtgccaaagg	gggtgggagg	aattggagca	ggaagcttgc	ctaagtgtgc	ccagcaaagc	5400
cacggtagaa	ctttctactg	tggctctatg	ctacttctta	gcaaccttct	ccatgtgctt	5460
cctggagagt	ccttggagtc	agaacctttt	tcttgaaacc	cagacacttt	acttccaaga	5520
aaatgctgtc	caagaaaact	catccttccc	ttcttctcat	gaacgttgtg	tagaggtgtg	5580
tcttctcttc	ctttgagctt	ttccactcag	ggtttagggg	agggtgatatt	ctatatttgg	5640
gtttggctct	gggtactgca	acactagget	attaagattt	catccttact	gctttgcccc	5700
tcctatcttt	ccagaaaacc	acaatggatt	tgctagaaat	aatggaacgt	cctgtttgga	5760
caggatataa	ccatttctca	gctagaggat	attgttggaa	tgaagaaaga	taaatgggga	5820
gaagggaaact	cacattgctt	tggcacttaa	attaagccat	gtactgtgtt	gggaaattat	5880
ttatattatc	tcgttgaatc	cacagtagaa	cacagttgaa	caccatacaa	ggtaagtatt	5940
gtcatcctta	ttttaccatg	aggaaattga	tgccttagaga	gcataaaagc	ttggccaggg	6000
gcacatagtt	gggaagccgg	ggctaattca	tgcctgggct	ctttctgata	gttttctttt	6060
tttaattgtc	ccctctctcat	tgttaccttg	gggatttcaa	gagattcatg	tagcttctaa	6120
atcaacgaac	tgattcctgg	agagcagctt	ctgtatgaga	aaaatctagc	taattattta	6180
tttcagtgtc	tctggaatgc	aagctctgtc	ctgagccact	tagaaaacaa	tttgggatga	6240

caagcatgtg	tctcacaatg	ctgctctggg	tgccagtgtc	gtgctgccag	ttgtcatctt	6300
tgaacaaact	gatgcagtgc	tggtttaact	cttcctcttt	ttggagtaag	aaacttttgg	6360
ggcctgtgtc	cttctagaag	tttgcgtgagc	aaatggtaag	gaaaagaaat	aggtccctaag	6420
gcttgactat	ttcagagaat	ttcttgattt	attggactgt	caatgaatga	attggaatac	6480
atagtggtag	gctgtctttt	cttctcagac	actgcaattt	cctccaatct	cttgactttt	6540
ctagaagt	taatccaagt	ccttggtggg	tggtagataa	aagggtattg	ttctactaga	6600
gactgacctt	ggcatggaga	tctcatttgg	actcacagat	ttctagtcta	gcgcttgggt	6660
ttgtatccat	acctcgctac	tgcattctta	gttccttctg	ctccttggtc	ctcatgcccc	6720
gtgtcccacc	ctaccttgc	ccctactcct	ctagaggcca	cagtgattca	ctgagccatt	6780
tcataagcac	agctaggaga	gttcatggct	accaagtgcc	agcagggccg	aattttcacc	6840
tgtgtgtcct	cccttccatt	tttcatcttc	tgccccctcc	ccagctttaa	ctttaatata	6900
actacttggg	actattccag	cattaaataa	gggtaactgc	tggatgggtg	gctgggatac	6960
acagaatgta	gtatcccttg	ttcacgagaa	gaccttcttg	ccctagcatg	gcaaacagtc	7020
ctccaaggag	gcacctgtga	cacccaacgg	agtagggggg	cgggtgtgttc	aggtgcaggt	7080
ggaacaaggc	cagaagtgtg	catatgtgct	gacctgggga	gcttgtttgt	cggtttcaca	7140
gttgatgccc	tgagcctgcc	atagcagact	tgtttctcca	tgggatgctg	ttttctttcc	7200
agagacacag	cgctagggtt	gtcctcatta	cctgagagcc	aggtgtcggt	agcattttct	7260
tgggtgtttac	tcacactcat	ctaaggcacg	ttgtggtttt	ccagattagg	aaactgcttt	7320
attgatgggtg	cttttttttt	ttttttttga	gacagagtct	cgctctgtcg	ccatgctgga	7380
gtgtagtggc	acaatcttgg	ctcactgcac	ctccgcctgc	caggttcagc	gattctcctg	7440
cctcagcctc	ccaagtagct	gggactacag	gtgcctgcca	ccatgcccag	ctaatttttg	7500
tatttttagt	agagacgggg	tttcaccgta	ttggctagga	tggctcgcgt	ttcttgacct	7560
cgtgatccgc	ctgcctcggc	ctcccaaagt	gctgggatta	taggcttgag	ccaccacgcc	7620
tggccgatgg	tgctttttat	catttgaagg	actcagttgt	ataaccact	gaaaattagt	7680
atgtaaggaa	gttcagggaa	tagtataagt	cactccaggc	ttgaggcaaa	atttacaat	7740
gctgctgact	ttgtatgtaa	ggggaggcat	tttcttagaa	aagagaggta	ggtctctggg	7800
attccagtat	gccatttcca	tcctcagtgt	ttttggccac	ctgagagagg	tctattttca	7860
gaaatgcatt	cttcattccc	agatgataac	atctatagaa	ctaaaatgat	taggaccata	7920
acacgtagct	cctagcctgc	tgtcggaaca	cctcccgagt	ccctctttgt	gggtgaaccc	7980
agaggctggg	agctggtgac	tcatgatcca	ttgagaagca	gtcatgatgc	agagctgtgt	8040
gttgagggtc	tcagctgaga	gggctggatt	agcagtcctc	attggtgtat	ggctttgcag	8100
caataactga	tggctgtttc	ccctcctgct	ttatctttca	gttaatgacc	agccacggcg	8160
tccttgctgt	gagctctggc	cgctgccttc	cagggctccc	gagccacacg	ctgggggtgc	8220
tggctgaggg	aacatggctt	gttggcctca	gctgaggttg	ctgctgtgga	agaacctcac	8280
tttcagaaga	agacaaacag	taagcttggg	tttttcagca	gcgggggggt	ctctcatttt	8340
ttctttgtgg	ttttgagttg	gggattggag	gagggagggg	gggaaggaag	ctgtgttggt	8400
tttcacacag	ggattgatgg	aatctggctc	ttatggacac	agaactgtgt	ggtccggata	8460
tggcatgtgg	cttatcatag	agggcagatt	tgcagccagg	tagaaaatag	agctttgggt	8520
tgtgctactg	cccaggcatg	agttctgctc	cctaggacct	ggctccgaat	cgcccttgag	8580
cacccactt	tttctttttg	ctgcagccct	gggaccacct	ggctctccaa	aagccctaa	8640
tgggcccctg	tatttctgga	agctgtgggt	gaagtgagtt	agtggcccca	ctcttagaga	8700
tcaatactgg	gtatcttggg	gtcaatctgg	attctttcct	tcaggcctgg	aggaatataa	8760
taactgagac	ttgttttatt	tctgcagagg	gttctaagcc	attcacttcc	cagatgggcc	8820
aataatgctt	tgagtaatct	ggagatcatc	tttaatgcgc	aggtgaatgg	aactcttcca	8880
cagagggatg	tgagggctgt	agagcagagt	gaactccctg	aaactcagac	gtcagctctt	8940
tgtctctcta	tctctgaaca	cccttcttta	gagatcccat	ctctaggatg	catttctctg	9000
tagttagttt	ctaagtctct	tgttctgtt	ctgcctttat	ttttttttcc	tggattctaa	9060
gccagtatcc	ccacttggct	gtcttaatgt	agcttaacat	gtctgtaatc	aaaatgatca	9120
tctttctgag	attcaaaggg	ctataaggga	ctttggagag	aatttcattc	agttttcctc	9180
aaactagaat	aatgcttgca	ctgtctgtaa	aagaacaaaa	gtgtcaaagc	atccttttgt	9240
tcactaaatt	tcctttttta	ttatagtgtt	acttaaatat	taggaagtta	aaagtaggta	9300
taaacttctt	ataggctgtt	attatacaac	tatatgaccc	atacatattt	acaaattaa	9360
tgcagccaaa	attgcaaaat	caataccatt	caaattaata	ccttaaatgt	ggtagggcag	9420
ctgttgttca	actgaaacca	aattataagt	tgcattggcag	taaattgctat	catgctgac	9480
atatttgagtt	tggccagtct	atattatcat	gtgctaata	ttgaattctc	cacccatttt	9540

tctacttgta	tgaccttaat	ttgatggcac	ctgttccatc	ctcatgagtt	tgctacaatt	9600
atactgggtgc	caacacaatc	ataaacacaa	atataaactt	gggctttgaa	atcttgtgcc	9660
agaacttggc	tttaaagtaa	gcatttaaaa	aatccatag	tgtttattag	actttgttta	9720
gatgactggt	gaaatgaaaa	caaagtgttt	aaaatcctct	tagagaactt	aaatataatc	9780
cctcagcaat	atgtatacag	atcttccttt	gagaaaaact	gattgtgttc	agcctctcat	9840
gttacaaatg	gggaacctga	attctgaggt	ctctagttag	agaacagggg	ctggaatctg	9900
tggatcctat	ctgttttaat	aataattgta	aagtataata	gataatatta	tattaaaaag	9960
agagnnnnnn	acacttagaa	tgagcttcca	tgtgtgaggc	actaactgat	taggcattat	10020
taactagatt	tattcctttt	aaggcccccgc	gatgtactgt	tatttccaca	tgttgtagct	10080
ggggaacgtg	ctactcagag	agggttaagta	acttgtctga	ggtccacacc	actaacaagg	10140
agcacaggta	gggttcaaat	ccagataatc	tgactttgga	gctggcactc	taactcaatg	10200
tgcctaateg	cttttcagtg	gtgtcattat	tttgccctatt	ctccatctga	gaatattgaa	10260
gtttctgaact	ccttccttgc	ctttctccct	gcctcccgtg	gttatcccca	ggctctgggtg	10320
ttccagtcct	ctatgtccgt	ccttactctt	attcctttgc	tacagtgtga	tccagggctc	10380
ctgcccttct	tatcctggta	gagggggccc	acttgcctggg	aaattgtctc	cgccatgggt	10440
tatccatggt	gtgtgtccat	tagtgagtag	tgggaagaat	catatcatgt	tggcaatgaa	10500
aggggggcta	tggctctggg	gtagtctagt	ctgaactctt	atctt		10545

<210> 15

<211> 4736

<212> DNA

<213> Homo sapiens

<400> 15

cttttttttt	tttttttttt	tttttttttt	tgaggtgaag	tctcactctg	ttgcccaggc	60
tggagtgcaa	tggagcgatc	ttggctcacc	ccaacctctg	tctcctgggt	tcaaacagtt	120
ctcctgcctc	agcctcccgga	gtagctggga	ttacaggctc	ccgccaccat	gccagctat	180
ttttttgtat	tttcagtaga	gatgggggtt	cacccttttg	accaggctgg	tcttgaactc	240
ctgacctcat	gatcaaccca	cctcagcctc	ccaaagtgtc	gggattacag	gtgtgagcca	300
ccacgcccg	cctcataagt	atcttctaaa	tttattttaca	gtcatgccat	ttaaaaggaa	360
agttgtattc	ctgtctttgt	taatattttat	aagtgatttt	attcagctac	aagcttggaa	420
tggcatataa	ttttgtattc	tgcttttttc	acttaatat	acatggctaa	tgattttctgt	480
gtttcataaa	cattattctg	atgatggcat	gatatattgt	tgagtacatg	taccataatt	540
gaatcatttc	cctattgcta	tgcaattaa	ttgtttccaa	tattttgcaa	ttataatgtt	600
tcaatgaatg	aataacttta	tgcatataga	tttttgat	cttaagtcca	gtttcctagg	660
atgaatttcc	aggaatagta	attggggcaa	tgggataaac	atgactcttg	aatacgtatt	720
gttaacattg	ctttcccaaa	gggctcaact	gatttatatt	tccgtgttca	ttatctttta	780
aaccagctca	tttactcacc	aaacattttt	aaagccatta	tcatgtggta	ggcttagtaa	840
gaagaaagtg	accctaagg	agaagcttat	atataaatag	ggtccttgg	gtaccaagt	900
ctgatacaga	cacaaagtag	ctggggaaat	tgagatgagg	gagtcctggc	tcagctggga	960
gaaaagttca	ttttcataga	gtcatgggtt	tggtcttttg	cagaaagaaa	attgctttct	1020
tccccacccc	cacccccagc	tttattgagg	tataattgac	aaataaaaaat	tgtatatctt	1080
taagatatgc	aatgtgat	atatgtatat	ctcaacttaa	aaaataagct	acagaataaa	1140
aagggtgttg	ctattaaaaa	aaaagaaaag	gctgaatgtc	attcccaagc	ttggaaattt	1200
gagtaggtg	cctctttggg	attattttaca	gaaatattag	caagaccagc	cccattcttg	1260
gtcttgagta	ctccactgtc	agcatgcttt	cttccagaga	gggatccatt	tgcttttatt	1320
tttcattctg	ttgtgccgtc	tatgcaaact	attcttgata	gttttatggg	aacagtgttt	1380
ttttgttcca	tgagataaat	ttatacatgc	tcattgtgga	aaatttagaa	aagacaggaa	1440
agtattaaaa	acatcmeytt	tttttttttt	tttttttttt	tttttttamg	cagacagagt	1500
cttgctctgt	cgcccaggcc	ggagtgcagt	ggcgtgatct	cagctcacag	caacctccgc	1560
ttcccagggt	taagtgattc	tcctgcctca	gcctcccaag	tagctgggag	tacaggcatg	1620
caccaccacg	cccggtctaat	tttgtatttt	tagtagagat	ggggtttcac	catgttggcc	1680
aggctggtct	caaactcctg	acctcaggtg	atccgcctgc	cttggcctcg	caaagtctctg	1740

ggattatagg	caggagccac	tgcgccagcc	acacctacgt	tcttatcatc	ctagtacatc	1800
cactgtcatt	atcttgctgt	atttccttct	gccagtcctc	actctgatca	tgcagtggcg	1860
tgatcatgca	gtgatctcgg	ctcactgcaa	cctaggcctt	ctgggttcga	gtgattctcc	1920
tgccttagcc	tcctgggttc	aagtgattct	cttgccttgg	cctcccaagt	agctgggatt	1980
acaggcatac	acccccatgc	ccatctaatt	tttgtatttt	tagtagacac	agcgtttcac	2040
taaaattttg	tatttttagt	agagatgggg	tttcaccatg	ttggccaggc	tggctctcaa	2100
ctcctgacct	caggtgatcc	gcctgccttg	gcctcacaaa	gtgattacag	gcatgagcca	2160
ctgcatccat	cgccaaaaag	atttttttaa	agagtttaat	gtagaacccat	atcaaaggctc	2220
tttggaata	aaaaacagtt	ttttaaaaaat	atcagaata	aaacaacaaa	taaataaata	2280
aataaaaaaca	cccaaaaacaa	tctgaagcac	gagcacctag	cagaaagggtt	caattatgat	2340
ctattcatag	agtgggaatat	caagtagaca	ttacaggaca	tgttttaaga	ttatatttta	2400
tgatcatggga	aatgctctcc	cagtatgatg	ttaaatgaaa	aaacagaata	caaaagtata	2460
tatgctgcat	agtctcaata	ttgtagagaa	aaaatattat	ttatgtatgc	atgaaaaaag	2520
acaaaagatg	ttaacagaga	tccattgtta	cttcagttta	ctagggattg	tctctgggag	2580
gtaggattaa	ggtgattttat	atttaccttt	ttaaactttt	ctgtattttt	ttattttcaa	2640
attttccata	aaaatataag	gacttgaaga	tcaagaaaaa	atctctgctt	tggctcagtg	2700
cagtcgtcac	gcctgtaatc	ccagcagttt	gggagcccta	ggggagagga	tcacttgaac	2760
ccaagagttt	gacgttccag	tgagctatga	tctccggatc	gtaccgcctg	gacgatggag	2820
caagaccctg	tctcaaaaaa	aaaaatcttt	gctttttttt	tttgtttgtt	tttgagacgg	2880
agtctctctc	tgttgcccca	gctggagtac	agtggcacaa	tctcagctca	ccgcaacctc	2940
tgcctcctgg	gttcaagcga	ttctcttgcc	tcagcctccc	aagtacctgg	gattccatgc	3000
accaccact	atgccagct	acttttttgt	attttcagta	gagacagggt	ttcaccatgt	3060
tggccaggct	ggtctcgaat	tcttgacctc	agctgatcca	ccggccttgg	cctcccaaag	3120
tgctgggatt	acaggcatga	gccactgtgc	ccagcccaat	cttttgcttt	ttttaaaaaa	3180
agaagacaaa	aagggatttt	ataccagtat	tatcttggct	gtgtgactct	gaagccacag	3240
ttgtaagtta	taattactct	gaaacacaag	gccctgtgac	tcttttgggc	tctttgggtg	3300
ttatcttgat	tacaacgttg	gaatatagaa	atgaaaggaa	tgggagagggt	gatagacttc	3360
aggcagtgta	actagtgtc	tgaacactac	tggctcaatt	atattgtgtc	tagtgatttc	3420
catcttgtcc	gtctgctaata	ttatcgcttg	tgactcact	gaggcagggt	tttccctttg	3480
agaaacctca	ttgttttaac	cagtgtatca	tgcttgttta	gaagttcaat	gatcttttta	3540
actcatcgga	gaagatgatg	accagacctg	gacagatggg	gaaggacttt	gcactctctc	3600
tttacagtc	tgagtgcaca	cagggtcaata	tggaaactatg	tgtgaatttt	cattgtcttt	3660
gagagccctc	ttctctgccc	catagggagc	agctttgtgt	gcaattagag	gagcaagggt	3720
tgtgtgtatt	tagcacagca	ggttggcctg	gtcctctcct	ctcaacatag	tcaccacata	3780
cctggcacta	tgctaaggct	gggaatgcag	acagatgggt	gcctgctttc	agagtgtctca	3840
atgtgctgag	gaagccagca	acagaaacag	atgatttcag	gagctccagg	aaaatgctac	3900
aggaggagtg	tgcttgggtt	actggagtag	cacaggagga	gggcttctag	ctcaggctga	3960
gatttttagta	aaggaaatta	tgccacgatg	aatcctgaag	aatgaataga	agtgaaccag	4020
ataaagcacg	ataggaagca	tcttccctta	cctaagggaa	gacacagagg	tatatggaat	4080
ggtatgttaa	aaggttggga	ctccaaacag	ttctgttaaa	gcttagagag	tgggtgggaga	4140
gactggagaa	gttgattaat	tagtaaatga	agttgtctgt	ggatttccca	gatcccagtg	4200
gcattggata	tccatattat	ttttaaattt	acagtgttct	atcttatttc	ccactcagtg	4260
tcagctgctg	ctggaagtgg	cctggcctct	atttatcttc	ctgacctga	tctctgttcg	4320
gctgagctac	ccaccctatg	aacaacatga	atgtaagtaa	ctgtggatgt	tgctgagac	4380
tcaccaatgg	cagggaaaat	ccaggcaatt	aacgtgggct	aaattggact	tttccaaaga	4440
tgctgtcttt	gggaaacatc	acacatgctt	tggatcagaa	aacctaggct	tctaatttgt	4500
tgataaggca	tgaactcagg	agactgtttt	cagtcctagt	gaatgggtgat	aattgtaatt	4560
ataacagtag	acaacatctc	ttttacacat	tttaaatcat	gaaaatagaa	taaccttact	4620
gataatttta	gaaagtgggtg	attaaaagca	catttaagat	aatgccttaa	cacctagtct	4680
tttccatag	catgatgtct	taatcacaca	ttgcaaatca	tggaaacacag	aatttt	4736

<210> 16

<211> 4768

<212> DNA

<213> Homo sapiens

<400> 16

atcttacaat	cacagtcttt	ctcttagggc	tgggctcagt	gggtggattg	acactgcaga	60
aatggccaga	tctaaaggat	caacatttac	gtagctggga	aatgtagctg	ggacttcagt	120
ttcactgccc	tagtgatttt	tcctaccact	aagcagctca	gtccataccc	ctacgagacc	180
cacaagctta	tgagatactg	ttcttcagg	aaagcagtgg	ggccagggcc	accttttaat	240
tgtgtttctt	ggcctgggtcc	catctttctc	acaatatata	gcaacagtta	tttacttgct	300
gattttctaa	tgcacatcac	acatagtcac	attaaacaca	cacacacaca	cacacacaca	360
cacacacccc	tcaagaaaca	ttttctgaga	cgtgatttcc	tgatttcatc	aaaaaagaaa	420
agagcggggc	aggcacagtg	ggaagtcaag	gtgggtggat	cacttgaggt	caggagtttg	480
aaaccagcct	ggccaacacg	gtggaacctc	gtctctacta	aaaatacaaa	aattagccag	540
gcgtgggtggc	gcacacctgt	aatcccagct	actggggagg	ctgaggcagg	agaattgctt	600
caacctgcga	ggctgaggtt	gcagtgagcc	gagattgcgc	cattgcactc	cagcctgggc	660
aacagagtga	gactctgtct	caaaaaaaaa	aaaaaaaaaa	aaagcataaa	ctgaaattta	720
tatgcaattt	atatgcctgt	gagataattc	tgttttctct	tttggaaccc	caaagagatt	780
tttttgattg	atgagcaa	acatttttaga	ttttatttaa	gcattatgcc	aagcaccact	840
gaagtataag	tttcaagggc	aaactcagtt	ttttcatcta	ctagacgaat	gattttctgg	900
aatgattaca	agcaggcaag	atggtgtagt	ggaaatagca	aatgtcttcg	gcacagaca	960
agttgggggt	tgtttgatc	ctgcctctgc	ccttcaccga	ggttgtgatc	ttgggcagat	1020
tgttgagttt	taacctagat	tcctctgact	ccagatcata	aattttcaga	aaagttctga	1080
aattcttgta	tatactgatg	gtaaatgaga	cttttcctta	catctatgca	cttctttgtt	1140
tgtttgtttt	gagatggctc	tgctctgttg	cccagactgg	agtgcagtag	tgcaatctcc	1200
gctcactaca	atgtctgcct	cccaggttcc	agtgcagctc	ctgcctcagc	ctcccaaata	1260
gctgagacta	caggcatgtg	ccaccacgtc	cggctaattt	ttgtattttt	agtagagaca	1320
gggttttgcc	atgttgacca	cactggctctc	gaactcctgg	cctcaggtga	ttcgcccgcc	1380
tcagcctccc	aaagtgcctg	gattacaggc	atgagccacc	atgcccggcc	atatccatgc	1440
acttcttgca	accttacctt	cttttctcat	cacctccag	ggacctagtt	ggaagagcag	1500
agttaaaagt	taaggtgaaa	cttgagagg	tgtcttgctc	ctaggaacaa	aggactgggt	1560
tgaaattctc	tgtaaatctt	cccagttca	aaccagagtt	atcaaggtct	taaaaacttc	1620
cctgggtcct	gagagcccat	tatatattt	acttgctctc	ctgtacaccc	actgcctagt	1680
cctgatccta	cttttgtttg	caaataggat	ggggcacaa	gtacaaggaa	gggcctttgc	1740
cacctctgct	aagggataac	ctgaaatacc	ttcaccatca	ctgcctgtg	tgcttttca	1800
cctatgccag	tctgtctaca	gtgccagtgt	ctcctggcat	tgaaagggga	gaatcttttg	1860
gtcctttgag	tatttggttg	ggttacataa	atctccctga	atgaagagca	gctgacttag	1920
gcaagggggc	ttgtttggtt	ttccttgaa	tattaacagg	aagataggga	gattaactgt	1980
gtaaatgttc	aataggccag	agtccttgca	gaggggtggc	acagtgatca	gatcttatca	2040
catccttgct	ttgggtgttg	cctctctggt	tggagtatgg	atagaaaaga	aagaaagacc	2100
ctatattgaa	atgcaaagtg	cagcaagtcc	tgactttgga	ttaacttctc	agccccattg	2160
catgaaaata	aaaagatgaa	taaaacaagg	ttcccacttt	ggagggaggt	ggtagctgtg	2220
agatggaagg	agtgttcctg	ctgggcaaca	gcagagtaag	tgctggggta	gattcactcc	2280
cacagtgcct	ggaaaatcct	cataggctca	tttgttgagt	ctttgtccta	caccaggcac	2340
tctgcaaaaa	cgttttgctt	gcaaggctc	atgcgatgct	caccacagct	ctgtgaagtt	2400
aattgtactt	ttatcaccat	tttacagatg	agaaaactga	gggtatgggg	tcaatgactt	2460
ggctaaagtc	actgcttagc	aagctgcagg	gactggatgt	gaattccaat	tggtttgact	2520
ccaaagcctg	tgaagctact	tgttcttcac	cacctagagc	tgtggttctt	gataactgtg	2580
aactcttttg	gggtcacaaa	tagccctgag	aatatgatag	aagcaggagc	tctggccttt	2640
ctgtccatac	ctgaacagggt	ccttgggtta	agagccccctc	gtccagggcc	tattaactct	2700
gatcctcata	agcagcatcc	atgtattacg	gccgcaaacc	aaactgtgcc	agaccgaatc	2760
ctaggacca	gccccaatat	gtcccatcat	ccttttggtta	agaagctcat	tgtaagaaag	2820
aaagaggaga	gcaagaggat	gacctagtgc	atggggcctc	attgttttaa	ttagtacaaa	2880
aacaacaata	ataacaaca	aacccccgaa	gcttcacaga	tgacatcaga	ccccagcct	2940
gtgtgttttt	cagggtgccct	tgaggagctt	tgtagctggc	agaggaggtg	aaactgacaa	3000
atgtttggca	gatggaggag	agtaccagag	gggtttgaga	tgagctaaat	tccaacttaa	3060
ccgcagtgtt	gaggaagagg	cctggattgg	gaccatggag	atgggggttc	tactcccagt	3120
cacgccagct	gactttgcga	gtgttctttg	tcagtcactt	tatcttattt	tatttttttt	3180
tatttttttg	aaatggagtt	tcgctcttgt	cgcccaggct	ggagtgaat	ggcgcgatct	3240

tggtcactg	caacctcccc	ctcctgagtt	caagcgattc	tcttgctca	gcctccagag	3300
tacctgggat	tacaggcgcc	tgccaccaag	cccatcgaat	ttttgtatgc	ttagtagaga	3360
cagggtttcg	ccatgttggc	cagggtgggtc	ttgaactcct	gacctcaggt	gatccgcccc	3420
ccttggcctc	ccaaagtgtc	gggattacag	gcgcgagcca	ctgtgcccag	cccacttcat	3480
cttaccgtag	ttacctcctt	agagtatgaa	aaaatagggt	tagggcatcc	ccaagtcccc	3540
tctatgtctg	agagctgagg	ctggctgtca	aagaggaact	aaggatgcca	gggactttct	3600
gcttaggacc	cctctcatca	cttctccaac	gctggatca	tgaaccccat	tctacagatg	3660
atgtccacta	gattaagaat	ggcatgtgag	gccaagtttc	cacctgagag	tcatgtttat	3720
tcagaagaga	caggctctctg	ggatgtgggg	aatgggacgg	acagacttgg	catgaagcat	3780
tgtataaatg	gagcctcaaa	atcgcttcag	ggaattaatg	tttctccctg	tgtttttcta	3840
ctcctcgatt	tcaacaggcc	atthttccaa	taaagccatg	ccctctgcag	gaacacttcc	3900
ttgggttcag	gggattatct	gtaatgccaa	caacccctgt	ttccgttacc	cgactcctgg	3960
ggaggctccc	ggagtgtgtg	gaaactttta	caaattccatg	taagtatcag	atcagggtttt	4020
ctttccaaac	ttgtcagtta	atccttttcc	ttccttttct	gtcctctgga	gaattttgaa	4080
tggtctgatt	taagtgaagt	tgtttttgta	aatgcttctg	tgatagagtc	tgcagaatga	4140
gggaaggag	aattttggag	aattttgggt	attttgggta	tccatcacct	cgagtattta	4200
tcatttctgt	atgttgta	catttcaagt	ctgtctgtc	agctattttg	gaataacta	4260
tatgttgta	atgatatcat	gcagcagacg	tgcactgaa	tgggctggct	ctaggagcta	4320
gagggtagg	gctggcaca	agatgcattg	tgggaagggt	cttgcccata	agaagcttac	4380
agccaaggct	aggggagttc	tgtcttctct	gcactcaggt	acctctctca	cctctgtcac	4440
tgccccatca	gactacaatg	tctgcagggt	tttctccctc	gagtgtgagc	tccctgagca	4500
aagcaggatg	ctgccccttc	cctttgtatt	ccttgctcct	tgttccagt	cctgtacata	4560
agtatgggca	taataagtgt	cccccaaagt	agacattgag	gattcttcaa	atgcacagga	4620
ccgtgatgtg	agttaggacg	gagtaaggac	gatgggatgt	ggctcatgac	aatcctgagg	4680
aagctgcagc	tgcggcacgc	agggccacac	tgtcatgttc	atggacccta	gactggcttt	4740
gtagcctcca	tgggcccctt	ccatacac				4768

<210> 17

<211> 1295

<212> DNA

<213> Homo sapiens

<400> 17

tcatgactgc	cattgggtata	aagatgaata	taatccagac	cagattcatg	attattcata	60
catttttagt	gtattaactt	ttaattctgc	ttttaaaata	aattaaaaca	ttctaataatg	120
cccttaagag	tatcccagcc	caggccactg	agcctactgt	ggttcatgga	taagtgtgcc	180
cctgggggag	tgtgtgtgca	tgcatgtgtg	tgacatgca	tgatgagccg	ggccttgaag	240
gggtggaaga	tttgggtgtg	tagaccaagt	gagaaaggca	tttggggcag	tgatgatggg	300
tggggggagg	aacatgggtg	tgaatggagc	tgggtgtggg	gagccatggg	agtgggttag	360
ggccagcctg	tggaggacct	gggagccagg	ctgagttcta	tgcaactggc	agtcacttct	420
gtaaagcagc	agaggcagtt	ggcctagcta	aagcctttcg	ccttttcttg	caccctttac	480
agtgtggctc	gcctgttctc	agatgctcgg	aggcttcttt	tatacagcca	gaaagacacc	540
agcatgaagg	acatgcgcaa	agttctgaga	acattacagc	agatcaagaa	atccagctca	600
agtaagtaaa	aaccttctct	gcatccgttt	ataattggaa	attgacctgc	accagggaaa	660
agagtagccc	aggtgtcttg	ggcttgttcc	cattagatct	tccccaagg	gtttttctcc	720
ttggtggctg	gcctgtgggg	cccctctcca	ggaggcattg	gtgaagaaac	taggggagct	780
ggttgccaca	gacagtgatg	tactaatctt	ctctgggaag	acagaagaaa	agtccccagg	840
gaagaatact	acagacttgg	ccttagggac	agctaggggt	gcagattgct	gccaactgca	900
tttttctga	agttggccat	atgggtgcag	tgaatggatt	tatagacaga	gtatttctgt	960
gcatataaga	gcaattacag	ttgtaagttg	atatggataa	gtgaaagtta	agcacttctt	1020
tctaaaaaga	gaatgcaatt	cattttcccc	taatacttcc	aattagtctg	atgggcatth	1080
gaacttgttg	tctttaaaaa	gtgaaatctt	tacctctgat	ctggtaagta	tccaggaat	1140
ttcttgtgtg	ccaccagga	ggtatctggg	gagtgggcat	tttctgactg	aggcattggc	1200
tgccatagca	tcagagcagc	cttccaggca	gtggcctggc	aaggggacag	aggctgggtg	1260
gagcagctgg	ctgagtgcag	ccagtaatgg	catgt			1295

<210> 18
 <211> 2188
 <212> DNA
 <213> Homo sapiens

<400> 18

agctctccag	gtgattctga	tgcatactta	agtttgagaa	ccattgcttg	ttttgcatta	60
aacaggagat	tagtctctgc	agcttggtgg	aataaagctt	taaatctctc	caatcttagc	120
tctgtgaaaa	ggcagtgagg	agacaggaat	gaacggacta	gtgccacaaa	gctcaggtgg	180
ggtgggtgag	atcatttaga	agagaaagac	cgggcatggt	ggctcacgcc	tgtactgtca	240
gcactttggg	aggccaaggc	aggttggtatc	acaaggtcag	gagtttgaga	ccagcctgcc	300
tatcatgggtg	aaaccctgtc	tgtactaaag	ataaaaaaaaa	aaaaatttgc	cagtcattggt	360
gatgcatacc	tgtaatccca	gctactcggg	aggctgaggc	aggagaatct	cttgaacccg	420
ggaggcgggg	gttgacgtga	gctgagattc	caccattgca	ctccaacctc	ggtgacaggg	480
tgagactccg	tctcaaaata	aaaaaaaaaaa	aagaaaagga	aaggctgtgt	gtgtgtgtat	540
gtgtgtgtgt	gtgtgtgtgt	gtgtgtgtta	cagcaccatc	acactgtttg	agttgaggag	600
cacatgctga	gtgtggctca	acatgtttacc	agaaagcaat	atcttcatgc	ctctcctgat	660
atggcgatgc	tcccctatct	cattcctgtg	tgtgttttagc	caggcaactg	ttgatcatca	720
atattatgat	aacgttttctc	cactgtccca	ttgtgcccac	tttttttttt	tttttgagtt	780
acttactaaa	taaaaataaa	acactatttc	tcaatagact	tgaagcttca	agatttcctg	840
gtggacaatg	aaaccttctc	tgggttcctg	tatcacaacc	tctctctccc	aaagtctact	900
gtggacaaga	tgctgagggc	tgatgtcatt	ctccacaagg	taagctgatg	cctccagctt	960
cctcagtagg	gctgatggca	attacgttgt	gcagctactg	gaaagaaatg	aataaacctt	1020
tgtccttgta	atggtggtga	aggggagggg	ggtagtttga	atacaacttc	acttaatttt	1080
acttccttat	tcaggcagga	attgccaaac	catccaggag	tggaaatagc	aacctggcgt	1140
catgggccag	ctggttaaaa	taaaattgat	ttctggctta	tcacttggca	tttgtgatga	1200
tttctctcta	caagggatac	attttaagtt	gagttaaact	taaaaaatat	tcacagttct	1260
gaggcaataa	ccgtgggttaa	gggttattga	tctggaggag	ctctgtctaa	aaaattgagg	1320
acaggagact	ttagacaagg	gtgtatttgg	agacttttaa	gaattttata	aaataagggc	1380
tggacgcagt	ggcactgagt	tgagaactgt	tgcttgcttt	gcattaaata	ggagatcagt	1440
ccctgcagct	tgtgggaata	aggctttaaa	tctctccaat	tttagctctg	tgagatggca	1500
ctggggaaac	agaaatgaac	ggactagtgt	cacaaagctc	aggtgggatg	gacgagatca	1560
cttcaaagggt	ctgtaatccc	acgtctataa	tcccagcact	ttgggaggcc	aaggcgggaa	1620
aatcacttga	ggtcaggagt	tcgagaccat	cctggccaac	aatgcaaagc	ctgtctctac	1680
taaaaatatg	aaaattagct	cagcgtgggtg	gcatgctcct	gtagtcccag	ctactcgtga	1740
ggctgagaca	ggagaatcgt	ttgaacctgg	gaggcggagg	ttgcagttag	ccaatatcac	1800
gccattgcac	tccagcctgg	ctgacagagt	gagactccat	ctcaaaaaaaaa	aaaaaaaaaaa	1860
aagaatttta	taaaatcagg	aaataatatt	agtgtttatg	ttgaatttta	actttagaat	1920
catagaaaac	ttcctctggc	atcattatta	gacagctctt	gtgcagtggg	tagcaccaga	1980
cccagcttgc	atgggtattg	atttttcaga	gacacttttt	gagcttattc	tctggcagaa	2040
aggggaactg	cttcctcccc	tatctcgtgt	ctgcatacta	gcttgtcttt	acaagaagca	2100
gaagtgtggt	aaatgtttat	tcttgaaaat	aagctttttg	cttcacatga	tctagaattt	2160
ttaaaattag	aaaaatgtgc	ttactgcg				2188

<210> 19
 <211> 1183
 <212> DNA
 <213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(1183)

<223> n = a, t, c, or g

<400> 19

agtaaaatgg	agaattccaa	attctgaaat	tgtagaaca	tagttctgtg	tcttagttaa	60
atatcgacac	ttacagataa	atagcataaa	tgctttctcc	ccatatttca	gcccagtcct	120
acttaaagac	aacataaatt	gcaaaatagt	gaggatgttg	ttcatctaat	aaaagtggtt	180
ccaggaattc	agactctgga	ttcctgtttg	ccaaatcatg	tgccccactc	ttaagaaaaac	240
gagttggact	ntggattttt	ctttgcaaga	gggacaagag	tggtggagat	actgagttaa	300
tgcaacttgc	aggttttaag	tgctctgtca	ttgtgccttg	tgctttgata	cattctgagt	360
ttcagtaaag	agacctgatg	cattggactg	ttgcaatgga	acctgtttta	agatcttcaa	420
agctgtattg	atatgaagtt	ctccaaaaga	cttcaaggac	ccagcttcca	atcttcataa	480
tcctcttgtg	cttgtctctc	tttgcatgaa	atgcttccag	gtatttttgc	aaggctacca	540
gttacatttg	acaagtctgt	gcaatggatc	aaaatcagaa	gagatgattc	aacttggtga	600
ccaagaagtt	tctgagcttt	gtggcctacc	aaggagaaa	ctggctgcag	cagagcgagt	660
acttcgttcc	aacatggaca	tcctgaagcc	aatcctggtg	agtagacttg	ctcactggag	720
aaacttcaag	cactaatgct	ttcggaatgt	gaggcttttc	cttggacagc	atgactttgt	780
ttttagaaaa	agtacggctg	gctgggagtt	tgtgatataa	tttagttcag	tggtattcta	840
agtgttctta	gtgttctttc	agacttttgg	gccatctccc	aaaggggtgaa	tggaagaat	900
aagctgggtg	tggctgagtt	taagccaaaa	gttttttgtg	cttgtttcaa	tcagagaaga	960
cctgcttttt	catgttttta	ctattataat	actaagcaag	agctcatttg	aaaacagagt	1020
tcttcatatt	taaaaaaaaa	aagtcttgaa	accattgatg	ggaagatgga	tatctattta	1080
tgtttaaaaa	cccatcataa	agatgacatt	gtgggctgtc	acagttggaa	ggccctggaa	1140
ttagatgaga	ccacactatt	tagcttactt	agtaataaca	ttg		1183

<210> 20

<211> 8981

<212> DNA

<213> Homo sapiens

<400> 20

ccgtttggca	aatgctcagt	aaaagaaaag	ggtagaagg	ggagaaaggc	attttatccc	60
aagccttcag	gaatcaggat	gaggatgtct	tcaccttgtg	gtggggagta	attatacaat	120
tagagacagc	acattggagt	gtggctgata	tgctgtgtga	tgatagctct	agctctctgc	180
ctagcagagg	aaggacattt	caatagaaga	aaaagttaa	gaccttgccg	agaaacagag	240
aaaggatgtt	tgtcttttta	agaagttgaa	aaccctgttt	gcagacaaaa	gccctccagt	300
tttggcagta	aactttcatg	caagggaaga	aaaaggcagg	ggatgacatt	gttgacaatt	360
gtgaggaatt	accatgtgcc	aggcactgtg	cgaggggctt	tgtacatatc	ctctagtttt	420
agtgtctata	aaaactctgt	gatatgtgca	cagcatttta	aactttgctg	catagtgcag	480
aaaatggaag	gatggggaat	ttgagtcatt	tgcccagggt	tctatagcta	ccccagggtc	540
ccatgactgg	agaattgggg	cacagggtgg	cgggggagag	tgagtgacaa	gaatcctaac	600
aatcttattt	ccattgagtc	cttataaaag	aagtggatta	actaccacgt	ttttaagttt	660
ttcttaaat	taggttatgt	ggatctggcg	ttcttgttt	tgctctgggt	ttgttttgtt	720
tttgctatgc	tgtcttgaac	atctgtcatc	ttgtaggcct	aacggtaaac	acaaaaacac	780
tttacctcct	atagctttca	attaagatct	ctcagtttgt	gtttgtaata	gttttccagg	840
caagttctcc	ctaggttcgg	cttctagtgt	gttaaccttt	agttataaag	tgaacccaaa	900
gagagaaagt	agaaacaaaa	cacctcacct	gtttttgctc	atgaattact	ctctatggaa	960
ggaacaatca	tgaacacctc	tgcgatatcac	agaggcctat	ctgagtctga	cgtttaaggg	1020
agaccgcgta	ggctcccttg	aggactgtga	atgtgggagt	cctgggactc	tggtgaagaa	1080
cccgttccag	aagagatgaa	tgagctggac	aagttctttc	atagaacctt	taggcagggt	1140
ttcttagaaa	tgcacattga	ggattatgct	tggatattgt	gatgatcaga	atgatactca	1200
atcccttctg	catttggaa	tctctttgaa	agaaaacatc	ccaggcagct	atttctcaga	1260
gatagtgcgt	cccagccact	tctagacatt	ttcttgtgta	gtctacatta	taatttcaca	1320
gcagtctctg	atatgacaaa	tgtaaaaata	gcccacacct	ctctaaactt	cagagatgtc	1380
tgatatgata	ttgaataaaa	caatgctcat	agaaacatca	agaaagggtg	attttccctg	1440
gatacttttt	tcctgcttga	caaataacag	tgaagaaact	gatctcacgt	ctttttctct	1500
ttggaagcct	gaacactcag	aacccaactt	gaggctcctc	agctatagca	attctgactt	1560
cacagtctgt	aaattattgt	tctttttttt	cttttagctta	tgctttctgc	cctaatttat	1620
cttttccctg	ttctaataaa	ttattgtcct	atatctgctg	tgcaagtagg	tgacatataa	1680

cagcaattaa	atatatgaat	tggtacatat	aaagatttga	ctaaaactcg	atgtaaaaat	1740
aagtgttcta	cattcaattt	ccagtgttag	aaacagtgtc	gacttgaaca	gagtgcacaga	1800
attccatctt	tccctatatt	tgacagcttt	aaactttata	ttttcttcct	ttcttgtgag	1860
cogtcattaa	cttgtttctc	aaagccattc	ccgtattacc	catcttgcag	acgcagacag	1920
atttgggaat	ttgcggtcag	agttgtattg	gacacatccc	cccagcccac	atgagatcct	1980
tttaattctat	tgcatattaa	ctagttttaa	gtacaatatt	cctacttcat	ttaaaaccat	2040
taatcaaaga	atgagtttga	aaatgaacaa	aatgcaaact	tacagttaga	aataattgta	2100
gtgtcttttag	ttttgggttag	gagtcggttt	cttgtttgtt	aaactcaaga	ttgtgaacag	2160
ttttaattca	cttgtttatt	tccaatagag	atttcagggt	tacatttgaa	ttcagaaaca	2220
aagttttctt	tctcattaca	gagaacacta	aactctacat	ctcccttccc	gagcaaggag	2280
ctggccgaag	ccacaaaaac	attgctgcac	agtcttggga	ctctggccca	ggaggtaagt	2340
tgtgtctttc	cagtaccagg	aagcggatca	tccactgtat	cagtattttc	attcctgagt	2400
ctggcaagag	gtccttttga	gttgaatata	acatgggatg	taatatcaat	tttcaaagta	2460
taagtgatgt	aaacaataat	gttttgattt	ccttatttta	gaaatgaaga	aacctaaaac	2520
tcatagatgt	ctcagagcta	attgggttagt	ggctaacagc	tggatatcta	gtttagaacc	2580
ttctccattt	tttctttttg	cccctaggta	atcatacatt	tgtaaagagg	agaattatct	2640
ctggccactg	ccatgcactg	cttttgtctg	accagcaatt	tctccatatt	gcttcttcag	2700
tagcaaggcc	aatcatttta	ccaacacaca	tgtttgctaa	ctaacaggaa	taacgtggta	2760
cccctaattc	agccctttcc	cttgaaagca	tctggcttct	gaggttcaac	tatgggaata	2820
tggtctctta	atgaacatta	agttgagttt	gccttttagg	tccacatggt	gacaaatgta	2880
tcagagtaat	ctctgtccta	ggatcagagg	gcctgtaggc	acttgcaaaa	gcagttagct	2940
ctgactccca	gccagtgcac	actccacctt	tctgactccc	agccttgtct	caaattaggc	3000
ttggaagcga	ggaactgtct	ggtgtccccc	agcataggaa	gctgagccag	ggggcagtcg	3060
tcacaaacaa	tacagacttt	aacgtgtagg	atattggaaa	ataataattt	gtggggaaat	3120
tgtctcagac	ttggtccacc	cttattttta	gctgcttctc	taatccgttt	ttcttttttt	3180
ggtgcttgta	tctaacctac	ccattttttg	gtgcttgcac	cattttttca	aatatcaaaa	3240
acgaacttta	tgttttctaa	caatgaaagt	attgcatgtt	cattgtggaa	aatgctgaag	3300
acttggaaaa	tacaaaaatg	ctgagatcaa	acactattga	tacgttagtg	tatttcttcc	3360
tgtcctgttc	tactttcttt	ctttgaattc	tgtcacgtg	tttctgactg	atgaggtctg	3420
acttttgggt	tccttttcca	gaggagaagc	cttctttctg	cttgccattt	gttaccctgg	3480
ttatgaaggc	tggtaacctt	ttttactagg	tagagaagct	ggaccaactg	gggttcttcc	3540
agggggagaa	tgagaaagag	aaactgtttt	gcaagtccgt	agctattttc	ctagggccct	3600
gttagctgac	attgacatgc	cttgcattgc	tctgcagatc	ccctcgcagc	cctctgtccc	3660
ttgttcattt	ctggcccttag	agaaagcaaa	gcagggtctg	taacagggga	ggctgcctct	3720
aaactcaggg	tttggttaca	gctgttttca	cttacatcac	tggccctggg	tttttttttt	3780
tttctggcat	taaaaaaaaa	aattggaagc	aggtgatgtt	cccattgctg	atgtggtgga	3840
aactctccaa	gtgaacaata	tacgtttttc	ttggcagctg	tttcttgtgc	cctgcttget	3900
cctgggtccag	gacaagcaag	gaccatctgc	ctctttcaat	agaacacctc	cagatccctt	3960
tgatcaaaaag	ttactcattg	tctgacttgc	tatttctgtg	agataaatgg	gagaagatca	4020
ataaatgcac	ttgtttgtcc	agtcagcgtg	tggaaaagttg	ataattttga	ccaaagcaca	4080
accctgaaag	gaaaagaaaa	agggagtga	tgtcttctga	gaagctgcct	aggttcagac	4140
agtgctcccc	atttccctgt	atgctccaca	tgacaaacct	gagtgggtct	catcatgtcc	4200
attttgcaga	tggcaccaag	gctcagaaag	gttaggcaac	ttttccagtc	acccaatgag	4260
ttaattgaca	aaactgggat	tcaaaccag	aactgttggg	ttccaaagcc	tgtgttgttg	4320
cctgcttcgt	gaaaaactcc	agtagcgact	ggaatagaaa	ggagaacctt	ccaagaaaga	4380
aaatacgcac	tagcagaacc	tggaaattgg	gaggaaatga	ggacttgagg	aataagatga	4440
atgaaagctg	acctgagttt	cacatctggg	tgatgggaag	ggaggacagg	gaggcagcat	4500
ctcagatgtc	caccagcac	cgaccagctg	cctggcattg	ctaggtgttg	aggactcagc	4560
agtgaacacg	ctaacttctc	tgctttcttg	gggcacgtat	aggggtgagag	acagaaaacaa	4620
acaggtcagt	gtacaatgcc	acaggaggga	tatatgcagt	gaagaaaaag	cagggtaagg	4680
ggcatagagc	atgagaaggt	gcttttttta	aaggggktga	ttaggaaagc	tctctctaaag	4740
gtgacagttg	gacctgaagg	agatgatagc	atgtctgtgg	tgagggaagg	aaactccgaa	4800
caggaagaat	ggcagataca	aagacattga	tgctagagca	tgccaaagga	atgtgtttta	4860
ggaccagggg	aagtgaacaa	gtgggtgggg	gaggagagga	gctcagagca	ggaggaggtg	4920
agtgccatac	aggcctggca	agacttttga	ttcctgctgg	gtgagatgag	aatccagcgg	4980

agggcttgag	ggaggggaca	tgatgtgatc	tagagtttag	actgtttaca	ctctgggtgt	5040
tgggttgaga	agagactggg	atgggggaaa	gggaggacaa	aggacattgt	gctggattga	5100
gaaagcagta	agtcagtttc	attcattcac	tcaaccgatg	atgttcaaat	accaccatca	5160
tccgtgggct	aaaggatgaa	gagccatccc	tccctgagag	tcaggaagca	cttcccagat	5220
aaagtttgga	gtgtgagctg	aggtgtagga	gaaagagtaa	gagtttacct	ctgaaacggg	5280
tgctgggaag	agtcaatagt	ttggaataac	tcaataattt	atgggtgctt	tttagaaaaga	5340
tttgctggct	ttatgtggga	agaaatttkt	ttttttgatt	ggggagtggt	gggttggtgg	5400
tgaggctgcc	tgtggaaaaga	gaagtgagtg	ttttgactca	ctgttattta	aaaatctcta	5460
gggctgttcc	aataagcaac	aaaaggcaaa	atggcctggg	tctctgtccc	ctttctgtct	5520
gtatgcctcg	tacaggttat	gaaaagaaaa	agttgggaaa	agctgtccac	ctcacctaata	5580
tgtgttcttg	tggagtgtgc	tagatgcccc	ctctctggag	aaaaaaaaatc	cttgtggcct	5640
ctgaccacc	tctggagagc	ctagtccct	tctggaggca	gaaggcaag	cttaggacct	5700
agagagtgt	ggaccacgcc	actcacagga	accagcaggc	tgtgagggtg	aaagctaggc	5760
atatggagct	ttccaggctg	ggtgcagggc	ctcgtggccc	ttccctccc	ctctgtgctc	5820
tatagctcag	tcttcccagg	cgggtggaac	acgcagtgc	atctccagga	atacagggat	5880
ttattaatga	tttcttgtga	aatgtttgga	aatacaaat	actctataaa	tatttcataa	5940
tagcattggg	gctgagaact	ccacaaagt	ccggaataca	tttgcatgta	agacagaacg	6000
ctgcctgggt	cattgatgcc	tgttgagtgg	cagtcacaga	cactgcctag	gggttctgac	6060
tcacgctgtt	gggactgttc	tatgcagggc	accctcttgt	gtggcatagg	atctgtgacct	6120
caccacacac	tggtgtagct	ttgctgtctt	gatgatgagt	agagggcagt	gtccaggcca	6180
tggtataagc	atctactgcc	cccagggtt	accaaacca	agccaagttg	tgtctcagcg	6240
agctccgtga	agcatggaga	agttgagtac	tcagagacat	gacgtgactt	ttcaaaggct	6300
gtaagctgac	gagggacata	gctagggttc	agacttgagt	ttttcttttt	ctttttcttt	6360
ttcttttttt	tttaagactg	agtcttgctt	ttgtcgccca	ggctggattg	cagtgggtgct	6420
tggctcactg	caacctctgc	ctcccgggtt	caagcaattc	tcctgcctca	gcctccccag	6480
tagctgggat	tacaggcacc	tgccaccatg	cctggccaac	atttttgtat	tttttttagta	6540
gagatggggg	ttcaccatgt	tggccagggt	ggcttgaaac	tcctgacctc	aggtgatcca	6600
ccgcctcgga	cctcccaaag	tactgggatt	acaggtgtga	gccactgcac	ccggcccaga	6660
ctcgagtttt	tcactctaat	gctttttcat	tgccctgacac	tttactgaga	cttagcatagg	6720
gaacttcaca	tacagtacct	tttctcccaa	ggcggaagag	ggctgttcaa	tttctacact	6780
agagttcggg	gagttttaga	aatgagtcag	ttatcgagga	tgagagcagt	tcctgatagg	6840
ctcaaccaca	atgagatgta	gctgttcaga	gaaagcattc	ttttatctat	aaactggaag	6900
ataatcccgg	tgaaacgaag	cccagcccca	ggggcttcac	taactccagg	ctgtgcttct	6960
caaacttttag	tgagcatagg	aatcacctgg	gcatcttgtg	aagctgtaga	tttgaattct	7020
gcaggctggc	agaggggtct	cagaatccgc	atttccaaca	atgtctccag	taatgtgat	7080
gctgctcgtc	cctggaccac	agattgggta	gccagggtct	ggcaagctca	tcccaaggct	7140
ttgagatgac	atcagacaaa	atatgttctg	ggacatggct	tttgagagggt	caagaaaata	7200
agatgtttct	ttctcttctc	atccccaacc	cttgcaactgc	ccttttctcc	cttcccctac	7260
cctcctttct	gtcccatcc	ctgacgccag	ctgttcagca	tgagaagctg	gagtgacatg	7320
cgacaggagg	tgatgtttct	gaccaatgtg	aacagctcca	gctcctccac	ccaaatctac	7380
caggctgtgt	ctcgatttgt	ctgcgggcat	cccaggggag	gggggctgaa	gatcaagtct	7440
ctcaactggg	atgaggacaa	caactacaaa	gccctctttg	gaggcaatgg	cactgaggaa	7500
gatgctgaaa	ccttctatga	caactctaca	agtgagtgtc	catgcagacc	ccagccctgt	7560
ccccaacccc	atccctccct	tagttctggc	cttggcctgt	gtcatctcct	ccctctgtag	7620
cagcgtaga	tgtctacatg	cccatttgcc	caccagactg	agctcttctt	agaggagaga	7680
ggcttctctt	gaatagctac	ctgtccccag	ttctctgaat	gcagcctggc	acatctcagg	7740
tgcacagtag	tgtttatcaa	tggaaatgaat	gattgacagc	caaccttctg	gttttctggg	7800
ggatgtggaa	gggtggcttc	cagggtgatc	aagaatgaga	taatggcaga	aggacaaatc	7860
ctgcaagatc	tcacttatat	atggaatata	tgtaaggtag	aaagtgtcag	tttcacatga	7920
tgaataagtt	ctgggatct	tgatgtacat	cgtgatgact	atagtttagta	acactgtata	7980
gtatacttga	aatttgctaa	gagagttagat	ccgaagtgtt	cacactacac	aaaaaaggca	8040
actatgaggt	gatggattta	ttaacagctt	gattgtgggt	atcctttttac	aaagtataca	8100
tatatataaaa	catcacattg	tataccttaa	atatatacaa	tttttatttg	tcagttgtaa	8160
ctcaaaaaag	ctagaaaaagc	attttttaaaa	aggatgatgt	actgggtctta	atattaccat	8220
tgagataagc	tttataataa	cataaaaaaga	aataacagta	atgataatag	caacaacaac	8280

aacaacaaag	aactaacatt	taagtagaat	ttcttgtgca	ctgtgcattc	tgtttaagtt	8340
atctcatttt	accctcatga	taacctgcag	ggaagattct	ttaa'ccccac	atttcatagg	8400
ctcagagagg	ttaagtgcct	tggttagagc	cacatcagag	ttaatccaca	agagccagga	8460
ttcaagccca	aatctgcctg	gatctgtgct	ctctaagata	actgttagtg	gtggcgtgtg	8520
tgttctcaca	ctcagacatt	tgatctgccc	tttgtttccc	attcttagct	gcaaggcagt	8580
gttaaagaac	cctgtgtctc	catatccact	ccccacactt	aagcactttt	gtgggcccggt	8640
gtgccgtatg	cctcgtggca	gcagggatcc	aatgtcacag	ttttaggcag	tggcatcctt	8700
ttccttgaaa	acttgatgca	ggggaacctt	tctccatttc	caaccacagg	tgtgtctttc	8760
agacactgag	tgaggcaggt	tttgtacttt	attgtaacac	aagaaccttt	tcttctctgg	8820
agtaaagcac	tccagacatt	cgcaagttgc	tttacaagcc	ttaaaaggat	ggtattgtag	8880
gcaactttaa	ttaaatccca	tctcctcctc	tccccagct	tgcaagttga	cccaaggaag	8940
ccttcatttc	catgacagac	ttaattgtga	gggcatcctc	a		8981

<210> 21

<211> 20284

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(20284)

<223> n = a, t, c, or g

<400> 21

actgtgttag	caaggatggt	ctcgatctcc	tgacctcgtg	atccgcctgt	atcggcctcc	60
caaagtgcgtg	ggattacagg	cgtgaaccac	tgcgccctgt	tgagaatttt	tttttttttt	120
tttgggagaa	agagtttcgc	tcttgttgcc	cgggctagag	tgcagtgaca	caatctcggc	180
tcactgcaac	ctctgcctcc	tgggttcaag	caattctcct	gcctcagcct	catgcgtcac	240
cacgcccagc	taattttgtg	tttttagtag	agacagggtt	tctccatggt	ggtcaggctg	300
gtctcgaact	cccaacctca	ggtggttcgc	cgccttggtc	ctcccaaagt	gctgggattg	360
caggcatgag	ccactgcgcc	cagccccaaa	ttttggtttt	tgcttgaaaa	ctgagggtctg	420
aattcagcct	tctggttgcc	cctcaagagt	cagtttaaat	gttggtcatg	ttagttgtca	480
gtgaaaacaa	tgggtgaggct	ggcatgagag	tgtgaatctg	gatgggaggg	cttgtgcttc	540
atgaaaacat	ttttccagat	cagctcagtc	gtgagttatc	cgtcattgac	gttataataa	600
gctctgatta	tttatcaagc	atcattcttt	atagatatct	cagtttaatc	tgagataatc	660
ttctccacat	ctctccacat	agatgttatg	aattttactt	ttacagagga	gccaactgag	720
gctcagataa	gttacttatt	atatgactag	tagtggtaga	gctgggggtt	caactaagaa	780
ctctctggct	ccaaagccct	tgtaaagttc	tatcagtata	tgaccatgca	tatgagcatt	840
tgtctctcct	cttcttcata	gctccttact	gcaatgattt	gatgaagaat	ttggagtcta	900
gtcctctttc	ccgcattatc	tggaaagctc	tgaagccgct	gctcgttggg	aagatcctgt	960
atacacctga	cactccagcc	acaaggcagg	tcatggctga	ggtaagctgc	ccccagccca	1020
agactccctc	cccagaatct	ccccagaact	ggggggcaaaa	aactcaagggt	agcttcagag	1080
gtgtgcgcta	agtatactca	cggctcttct	ggaattccca	gagtgaaaac	ctcaagtctg	1140
atgcagacca	gagctgggcc	agctccccag	tcgtgggtat	agaatcatag	ttacaagcag	1200
gcatttcttg	gggatgggga	ggactggcac	agggctgctg	tgatggggta	tcttttcagg	1260
gaggagccaa	acgctcattg	tctgtgcttc	tctctctttt	tctgcgggtcc	ctggctcccc	1320
acctgactcc	aggtgaacaa	gaccttcag	gaactggctg	tgttccatga	tctggaaggc	1380
atgtgggagg	aactcagccc	caagatctgg	accttcattg	agaacagcca	agaaatggac	1440
cttgtccggg	tgagtgtccc	tcccattatt	accatgtgcc	tgcttgatac	tggagagggtg	1500
agtttctggg	cactttccca	ggtgtgagtg	aggtgagaat	tctttcagtt	tatctagctg	1560
ggggaaatgta	gtgagcatag	ctaaagtcac	agggcaccac	ctctccagaa	gtacaggcca	1620
tgggtgcagag	ataacgctgt	gcataatcagc	atccatgccca	ctcacgggtca	aatagcagtt	1680
ttctgcaaaa	cttagtgagg	gctgggtgttt	ggaagtggag	ttgagtaatt	gcagtaccct	1740

atttttcttt	ttgctgcagc	ctctcagcca	gccacagcat	ctccctgtgt	cttggtaggt	1800
tttgaaaga	agtgtgggag	caaaagcatg	atgttacatg	tagactggcc	tgagatactc	1860
attctcagg	cactgtgtga	atgatgagct	gctgttactg	tgtggagggg	aaatgcactt	1920
agtgcctcag	agccacttga	aagggataag	tgctctagag	acaattgggt	tcaaattgtg	1980
agcaggctga	gcaagaacag	aatgtctcct	ttgcctgagc	ctgagtgtctg	ttaatcacat	2040
cttctgcct	tgggctgagt	tagagaatca	ttagactatt	tcctgtttcc	atggtgaggg	2100
aggcctcttc	cttttgtctc	tgctccccct	aagaagcagg	tgaggatttt	gccagggttc	2160
ttgttttgaa	ccttattgac	tttaaggggc	gctgggtttt	agagactgta	cctacctagg	2220
gggaacactt	ccgaagttaa	ggactattcc	ctgatccgct	gggaggcagg	ttactgagga	2280
agtcctctta	aaaacaaagg	agttttatact	gagaaaagca	taaacagtga	tttgtatgga	2340
ttcacactga	ctaatatagc	tcattgccatt	aaagtggggt	ctcttctcta	aaggagggtt	2400
atatgatcta	gccccgtaga	cctaagtgtg	gtttcagacc	tgttcttctc	ggctctctcc	2460
ttggaatcca	tatttctact	agttggactt	tttctgtttg	tctggctctc	agaggattat	2520
aggaggccct	gtgaagtgac	tcagtgaatt	ttgattttgtg	ggcaagtaga	tggttcccta	2580
gtctgaaatt	gtcttgcct	taggtgtctc	aattcttcat	aaagctccag	ttcttaaagg	2640
acaagatcct	tgtaaacatg	gcaatggcat	tcttaggaa	tctagctggg	aaaatccagt	2700
gtgtatgctt	ggaaatgagg	gatctggggc	tggagagaaa	ggcatgggca	tgcttggag	2760
ggacttgtgt	gtcaagctga	ggacctttac	tttaagctct	aggggaccag	gcaaggggag	2820
atgtagatac	gttactctga	tggggtggat	gaattgaaga	aggatgaggc	aagaatgaag	2880
gcagagacca	gggaggaggc	tctccaagtg	gccaaggcat	aaagcaagaa	atgaggcctg	2940
gtgactgctt	agtggcagag	cagtgaagaa	gagggaggca	tcaaagttag	tctcgatttc	3000
tagctgggtg	ggtggttagc	atgtccagta	ggccagtggc	tactgaggtc	tgcaagtggg	3060
gaggggtggt	gggctggaga	cagatgatga	gggagtcctc	agcctgtggg	tgggaagaaa	3120
gggaacctct	tccaactgtt	ttctttgctt	cttccctctc	tttctctttt	tttttttttt	3180
tggacagagt	cttgcctgtg	caaccaggct	gaaatgcagt	ggcatgatct	tggtcacca	3240
cagcctccgc	ctcctgggtt	caagcaattc	tctgtctca	gcctccagag	tagctgggat	3300
tacaggcaca	tatcactgtg	cccggctaatt	ttttgtattt	tcagtggaga	tgggatttca	3360
ccatgttggg	cgggctggaa	tgaactcctg	acctcaagtg	atccacctgc	ctcagcctcc	3420
caaagtgttg	ggattacagg	catgagccac	cgcgcccggc	ctttcttccc	tctcttaaag	3480
agtgtttatt	taattccaca	aacatgagct	tgtcaccccc	tgtagcctgg	catctcctac	3540
acgaggtgat	ggctgaggct	tctgcttctg	ctggggtagc	tctgatcttt	ctgctttctc	3600
tggcactgtc	tacccatgtt	gcctcacccc	acaggtccca	gggcacctct	ctcgggcaag	3660
tcttggaaac	ctctgacact	gatttgcctc	cttttctgag	ctgcttttag	ccaccatcc	3720
tcgggacctg	ttttctctct	gcctccaccc	ctgcccggcag	tcttaggtct	cctgcccctc	3780
acgagcacc	cagagaggcc	acgtgctcag	tgatctcagt	gggcgcactc	ttctagtctt	3840
gctattcttt	ttggccatgt	tgttcagaaa	ccatactggg	cagggccgac	ttcacccata	3900
aggctgcgtc	tcttcaactc	gcttttgttt	gttccaaata	aagtggcttc	agaattgcta	3960
accctagcct	ctgtgaactt	gtgaggtaga	attttgtgtc	tgttatgtta	acaaaaatac	4020
atacatacct	tcctgggtgat	ggtataaatt	gctattctct	attggaaagc	aatttggaat	4080
gaaaatttaa	agaaccattt	taaaatatgc	tatcctgcgt	acctccattc	caccaccccc	4140
cagggatgta	gcctactgaa	ataattttta	agaagtcacc	atatgagaga	aaatgttatt	4200
gctatattgt	tattgtgaga	aattggaaat	agactaaatg	ttcagcacta	taggaataat	4260
taatgaaatt	acataatact	tatacaatca	ttatgctgcc	attgaaataa	taaatacaaa	4320
ggcgcaaggg	gggaaaagct	tataatgtta	gtgaaactaa	gactgatttt	tttataaagc	4380
agcagttttc	agacccttgg	agactccaat	tcggtagaac	cagagcttca	tcttctctgt	4440
cgaagctgtg	acaggagttg	caaatgcctc	tcctttttgc	tgagtttgca	gctgctgttt	4500
ttccggcagc	acatctgtgc	aggcctctgc	ctcgccccct	ctggatctgc	tgattgagca	4560
gcggattgat	ctgtccttct	ctttcgtgtt	gacccatgtg	aggaaccaac	tggcaagggg	4620
acaagaaatg	gaaaataggc	tcctttgcct	catgacctgt	acatcctgca	attggaaaag	4680
attgtacttt	agttggttta	accagcagca	ttatttttct	aaactaagca	gtaagaagga	4740
attaggtttt	atgtgggata	aacagactgg	gtctcaaaaag	aggaagggtga	tagaacacag	4800
tggggagggg	gaggtgcact	agaaacagag	ggcctatgct	ttcattcttg	ctttgctact	4860
taatagctgt	gtgacccaat	cttagagact	taacctctct	gaacttccat	tttctcatgt	4920
ataaaatggg	aaatattaaa	ggatactcac	tgggctgggtg	gcttgtgcct	gtaatcccag	4980
cacttggggg	ggttgagggtg	ggaggatcac	ttgagcccag	gtgttcaaga	ccagcccagg	5040

caacatggca	agactctgtc	tctatgaaaa	aattaaaaat	tagccagggtg	tggtgggtgtg	5100
cacctgtagt	cttagctact	tggtaggctg	agatgggagg	atcacttggg	cttgggaggt	5160
caaggctgcg	gtgagctgtg	attccatcac	tgcactccag	cccgggcggc	agagcgagac	5220
actgaatcca	aacgacaaca	acaacaaaag	gcaaaaaaat	aaaagtgtccc	tctttatgga	5280
gttgtgtgtaag	gtgaagcata	tacactattc	aacatagtaa	ctatataaag	gaagtattgt	5340
tggtgttact	gtagttaata	ccattaagtg	agatgtttcg	tatagtggaa	agcacatgga	5400
ctctgaattc	agactgggtc	gactttgagt	ctcagctcca	catctagtaa	tactatgacc	5460
aagccctggt	taaaatcatg	tttttttttc	ttcagcctca	gtcttctcac	atataaaata	5520
gggacactgt	catttacctc	agttttctgt	gaggataaaa	caacgacagt	gtatatgcaa	5580
gtattttgtgta	aattttgtag	tgctcctcaa	gatttagttg	gtgtttacta	cttgtacttt	5640
ctcactggaa	tggcagatgc	tggtggacag	cagggacaat	gaccactttt	gggaacagca	5700
gttggatggc	ttagattgga	cagcccaaga	catcgtggcg	tttttggcca	agcaccacaga	5760
ggatgtccag	tccagtaatg	gttctgtgta	cacctggaga	gaagctttca	acgagactaa	5820
ccaggcaatc	cggaccatat	ctcgcttcat	ggaggtgaat	ctgttgctgg	gatcatttag	5880
aaaagactta	acggcttctt	tctctgagac	gttacaataa	ggttcaggca	ggaggcaagt	5940
ttagaaaataa	tgatatgtct	catttacaaa	actatccctc	aagcctaaca	caggatttga	6000
taacaaaagg	cacttaataa	atgttagttg	agtgttgaa	tgagtaaata	aacttagct	6060
ttagtaaatt	aactctagct	tattctatat	aggctcaaga	gaatatttct	acctatttct	6120
ttctaggttt	tcctatctca	gtgactaatg	gtagcaaaagc	attcccttaa	aaaggcatta	6180
tttgtgaaac	ttayctaaaa	tcgaattcgg	gtccaattaa	atttttgaaa	ttttatatta	6240
aaaattatat	tagtagggat	gggtaagagg	tgttttggtc	tggttggttg	gttagttgct	6300
atgactcaga	attgctaaga	aaacagaaaa	gtaagataag	atcattgttt	taacctcttt	6360
tcctccacaa	aatcaataaa	taacatatcc	ctaaattact	cttagaattt	ctcttaaaatt	6420
gcagtgaaaa	acaaaaatcc	ttcattcttg	gttgaagggt	ggaaaactac	gttagagagg	6480
attagagaga	gaggatgagc	aatcgtgtag	tcagcccttg	cctcctagt	taggatttgt	6540
ctcagccact	gcttgtgtgc	ctggctgcca	acgttctcat	gaaggctgtt	cttctatcag	6600
tggtgtcaacc	tgaacaagct	agaaccata	gcaacagaag	tctggctcat	caacaagtcc	6660
atggagctgc	tggatgagag	gaagtctctg	gctgggtattg	tggtcactgg	aattactccm	6720
rgcagcattg	agctgcccc	tcattgtcaag	tacaagatcc	gaatggacat	tgacaatgtg	6780
gagaggacaa	ataaaatcaa	ggatgggtaa	gtggaatccc	atcacaccag	cctggctctg	6840
gggaggtcca	gagcacctat	tatattagga	caagagggtac	tttattttta	ctaaaaattt	6900
ggtagaaatt	tcaacaacaa	caaaaaaact	caacttggtg	tcattgatttt	ggtgaaattg	6960
gtacatgact	tgctggaagg	tttttcatag	gtcataaaaat	aacagtatct	tttgatttag	7020
catttctact	caagggaatt	aattccagga	attttgggtg	caggcacctg	taatcccagc	7080
tactcgggag	gctgaggcag	gagaattgct	tgaaccacag	aggcagagg	tgcatgagc	7140
taagatcgca	tcattgcact	cccgcctggg	caataagagt	gaaactccat	ctcaaaaaaa	7200
aaaaagatac	aaaaatagaa	aaaggggctt	ggtaagggtg	gtaggggttt	gggcaatttt	7260
tttttttttt	ttttttttta	ttgtatggtt	ctaaagggaat	ggttgattac	ctgtggtttg	7320
gttttaggta	ctgggaccct	ggctcctcag	ctgacccctt	tgaggacatg	cggtaactct	7380
gggggggctt	cgcctacttg	caggatgtgg	tggagcaggc	aatcatcagg	gtgctgacgg	7440
gcaccgagaa	gaaaactggt	gtctatatgc	aacagatgcc	ctatccctgt	tacgttgatg	7500
acatgtaagt	tacctgcaag	ccactgtttt	taaccagttt	atactgtgcc	agatgggggt	7560
gtatatatgt	gtgtgcatgt	gcatgcatgt	gtgaatgatc	tggaaataag	atgccagatg	7620
taagttgtca	acagttgcag	ccacatgaca	gacatagata	tatgtgcaca	cactagtaaa	7680
cctctttcct	tctcatccat	ggttgcccact	tttatctttt	tattttttatt	tttttttttg	7740
agatggagtc	tcgctctgac	gcccaggctg	gagtgcagtg	gctcgatctc	ggctcactgc	7800
aacctttgcc	tcccgggttc	aagctattct	cctgcctcag	cctccacagt	agctgggact	7860
acaggctcat	gctgccacgc	ccggctgact	ttttgtattt	tagtagagac	gaggtttcac	7920
catgttaccc	aggctagact	tcaactcctg	agctcaggca	atccaccctc	cttggcctcc	7980
caaagtgtctg	gatttacagg	tgtgagccac	tgcacccagc	ccaccacttt	aattttttac	8040
actctaccct	tttgggtcaaa	atttgctcaa	cttgcaagct	taaaatgtgt	catgacaaac	8100
acatgcaagc	acatactcac	acatagatgc	agaaacagcg	tctaaactta	taaaagcaca	8160
gtttatgtaa	atgtgtgcac	ttcttctccc	taggtggtaa	accacatttc	aaaacaaccc	8220
aaataaaaact	gaacaaagct	tcttcctctt	agacttttta	gaaaatcttt	cagtgtgtgag	8280
tcactaagct	gccaagttct	cattgtggga	actatgcctt	tggatgtaat	gatttcttct	8340

aagacaatgg	gcggaggtgt	agttattgca	gacatctgaa	atatgtaatg	tttcttccag	8400
attctggaaa	ttctcttatt	ctctgtggtt	gggtggtggtg	gtgggatgtg	tgtgtgtgtg	8460
tgtgtgtgtg	tgtgtgtgtg	tgtgtaggga	tcaggatgcg	ggaggagctg	ggttctgctt	8520
gtattgggtc	tctgttttgc	attgaatagt	gtgtttcctt	gtatggctat	ctatagcttt	8580
tcaaggtcac	cagaaattat	cctgtttttc	accttctaaa	caattagctg	gaatttttca	8640
aaggaagact	tttaciaaaga	cccctaagct	aaggtttact	ctagaaagga	tgtcttaaga	8700
cagggcacag	gagttcagag	gcattaagag	ctgggtgcctg	ttgtcatgta	gtgagtatgt	8760
gcctacatgg	taaagctttg	acgtgaacct	caagttcagg	gtccaaaatc	tgtgtgcctt	8820
tttactttgc	acatctgcat	tttctattct	agcttggaa	ctgaaacatt	gacaagagct	8880
gcctgaaatg	tatgtctgtg	gtgtgattag	agttacgata	agcaagtcaa	tagtgagatg	8940
accttggaga	tgttgaactt	ttgtgagaga	atgagttgtt	tttttgtttt	ggtttttagt	9000
actttaacat	aatctacctt	tagtttaagt	atcgtcaca	gttacctagt	tactgaagca	9060
agccccaaa	gaaatttgg	ttggcaacac	tttggttagcc	tcgtttttct	ctctacattg	9120
cattgctcgt	gaagcattgg	atcatacgta	catttcagag	tctagagggc	ctgtccttct	9180
gtggcccaga	tgtggtgctc	cctctagcat	gcaggctcag	aggccttggc	ccatcacctt	9240
ggctcacagt	tgtctttctt	tctccccctg	tccttctctg	gggcctccag	ctttctgctg	9300
gtgatgagcc	ggtcaatgcc	cctcttcattg	acgtctggcct	ggatttactc	agtggctgtg	9360
atcatcaagg	gcatcgtgta	tgagaaggag	gcacggctga	aagagaccat	gcggatcctt	9420
ggcctggaca	acagcatcct	ctggtttagc	tggttcatta	gtagcctcat	ctctcttctt	9480
gtgagcgctg	gcctgctagt	ggtcatcctg	aaggtaaggc	agcctcactc	gctcttccct	9540
gccaggaaac	tccgaaatag	ctcaacacgg	gctaaggagg	gagaagaaga	aaaaaaatcc	9600
aagcctctgg	tagagaaggg	gtcatacctg	tcatttctctg	caatttctatc	catttatagt	9660
tggggaaagt	gagggcccaga	gaggggagct	gacttgccca	aggtaacccc	agccgggtag	9720
cagctaagta	ggatgagagt	gcagggttca	tgctttccag	ataaccacat	gctcaactgt	9780
gccatgctgt	ctcattggta	gtggttcatg	gcagcatctg	aaagctatct	attttcttag	9840
atatattggg	tggcgattct	tcctaagttt	ctaagaacaa	taatcagaag	gatataatatt	9900
gttgccaggt	agactgtctg	gaagcagagg	ctgaaataga	gtttgatgta	tgggtatttta	9960
tgagggtcca	atacctatgg	aagagatatg	gaagatgcag	gattgggcag	aggaggaggt	10020
tgaactgtga	tatagggccca	accccggtggg	gcactctaga	gaatatgcag	cttgttggag	10080
ttgttcttca	tcgagctgaa	acatccagcc	ctttgtgctc	ccccaaaggcc	tccctcctga	10140
caccacctac	ctcagccctc	tcaatcaatc	actggatgtg	ggctgccctg	ggaagggtcgt	10200
gccccagggc	ctacatggct	ctctgctgct	gtgacaaacc	cagagttgct	gatgcctgag	10260
gcggtctact	gacagctggg	caacaaggct	tccttgaatg	gggactctgg	gcagtgcagt	10320
tttgtgtctg	aaccatacat	taatataattt	atatccgaat	tttctttctc	tgcaagcatt	10380
tcataataag	acacatcagg	taaaaaataaa	tgtttttgaa	gcaaaaggag	tacaaagaga	10440
taagaactaa	ctaattttaat	actagttacc	atctgttaca	aatagttcct	actgattgcc	10500
aaggactgtt	taaacacatc	acatgggctt	cttcttctat	cctcactaac	ccttttaaca	10560
gacaaggaaa	tgaggctcag	gaagggtcaag	gactttattg	aggttccaca	gtaggatata	10620
gttcttgcta	aaagcaaccc	ctccctcatg	ctctgttacc	taactgcaag	gggaagggtca	10680
gtggcagagg	tagtgggtccc	atgggttggtg	cataagagct	gctctgagac	aactgcagtc	10740
tgggtgggtcc	tgcagacatg	tacccatcag	ccggagatag	gctcaaaata	tccacaagag	10800
tttggtatgat	tgtgggaatg	cagaatccat	gggtgatcaag	agggaaagtc	aagttgcctg	10860
gccattttcc	ttggctttta	gacagaaaag	ttacgtggga	tattatctcc	cacagctctt	10920
ctgtgggtgcc	accagtcata	gtccttatat	aaggagaaac	cagttgaaat	tacctattga	10980
agaaacaaag	agcaaaactcg	cccactgaaa	tgcgtagaaa	gccctggact	ctgttgtatt	11040
cataactctg	ccattatattt	tctgcgtagt	tttgggttaag	tcacttatct	tctttaggat	11100
ggtaatgatc	agttgcctca	tcagaaagat	gaacagcatt	acgcctctgc	attgtctcta	11160
acatgagttag	gaataaaacc	tgtctttttt	ctgtagatca	tacaagttag	tgtttgggat	11220
tgttgaggca	gcacatttga	tgtgtctctt	ccttcccagt	taggaaacct	gctgccctac	11280
agtgatccca	gcgtgggtgtt	tgtcttctctg	tcogtgtttg	ctgtgggtgac	aatcctgcag	11340
tgtcttctga	ttagcacact	cttctccaga	gccaacctgg	cagcagcctg	tgggggcatc	11400
atctacttca	cgctgtacct	gccctacgtc	ctgtgtgtgg	catggcagga	ctacgtgggc	11460
ttcacactca	agatcttcgc	tgtgagtacc	tctggccttt	cttcagtggc	tgtaggcatt	11520
tgaccttctt	ttggagtccc	tgaataaaaag	cagcaagttg	agaacagaag	atgattgtct	11580
tttccaatgg	gacatgaacc	ttagctctag	attctaagct	ctttaagggt	aagggaagc	11640

atttgtgtttt	attaaattgt	ttaccttttag	tcttctcagt	gaatcctggg	tgaattgaat	11700
tgaatggaat	ttttccgaga	gccagactgc	atcttgaact	gggctgggga	taaatggcat	11760
tgaggaatgg	cttcaggcaa	cagatgccat	ctctgccctt	tatctcccag	ctctgttggc	11820
tatgttaagc	tcatgacaaa	ccaaggccac	aaatagaact	gaaaactctt	gatgtcagag	11880
atgacctctc	ttgtcttcct	tgtgtccagt	atgggtgttt	gcttgagtaa	tgttttctga	11940
actaagcaca	actgaggagc	agggtgcctca	tcccacaaat	tcctgacttg	gacacttcct	12000
tccctcgtac	agagcagggg	gatatcttgg	agagtgtgtg	agcccctaca	agtgaagtt	12060
gtcagatgtc	cccagggtcac	ttatcaggaa	agctaagagt	gactcatagg	atgctcctgt	12120
tgctcagtc	tgggcttcat	aggcatcagc	agcccccac	aggcacctct	gatcctgagc	12180
catccttggc	tgagcagggg	gcctcagaag	actgtgggta	tgcgcatgtg	tgtgggggaa	12240
caggattgct	gagccttggg	gcatctttgg	aaacataaag	ttttaaaagt	tttatgcttc	12300
actgtatatg	catttctgaa	atgtttgtat	ataatgagt	gttacaaatg	gaatcatttt	12360
atatgttact	tggtagccca	ccactcccta	aagggtactct	ataggtaa	actacttctg	12420
caccttatga	ttgatccatt	ttgcaaattc	aaatttctcc	agggtataat	tacactagaa	12480
gagatagaaa	aatgagactg	accaggaaat	ggatagggtga	ctttgcctgt	ttctcacaga	12540
gcctgctgtc	tctgtggct	tttgggtttg	gctgtgagta	ctttgccctt	tttgaggagc	12600
agggcattgg	agtgcagtgg	gacaacctgt	ttgagagtcc	tgtggaggaa	gatggcttca	12660
atctcaccac	ttcggctctc	atgatgctgt	ttgacacctt	cctctatggg	gtgatgacct	12720
gggtacattga	ggctgtcttt	ccagggtacac	tgctttgggc	atctgtttgg	aaaatatgac	12780
ttctagctga	tgtcctttct	ttgtgctaga	atctctgcag	tgcatgggct	tccttgggaa	12840
gtgggttggg	ctatagatct	atagtaaaca	gatagtccaa	ggacaggcag	ctgatgctga	12900
aagtacaatt	gtcactactt	gtacagcact	tgtttcttga	aaactgtgtg	ccaggcagca	12960
tgcaaaatgt	tttatacaca	ttgcttcatt	taattctcac	aaggctactc	tgaagtagtt	13020
actataataa	ccagcaattt	tcaaatagaga	gaactgtgac	tcaaagacgt	taagtaacca	13080
gctttgggtca	cacaactggt	aaatgttggg	acgtggagggt	gaatccactt	cgggtacact	13140
gggtcaataa	gcccaggcga	atcctcccaa	tgtccaccca	attctgtatt	tctgtgtcct	13200
cagagggggg	acaactagga	gagggttctgt	ttcctgagta	cagggtgtta	ataattaaat	13260
atactagctc	taaggcctgc	ctgtgattta	attagcattc	aataaaaaat	catgttgaat	13320
ttttcttttag	tacttctttc	ttaataataat	acatcttctt	gaccaagtcc	aagaggaaacc	13380
tgcgttggac	agttttcata	tgagatcaaa	ttctgagaga	gcaagattta	accttttttg	13440
gttcaccttc	tgatcctccc	ctaaggaggt	atacatgaaa	tatttattac	tcctgcctga	13500
acttctttca	ttgaatatgc	aattttgcag	catgcagatt	ctggatttaa	attctgagtc	13560
tttaacttact	ggctgaggga	ccttgagtag	gctccttata	cctcagtttc	ctcatcteta	13620
aaatggggat	ggcacctgcc	ccgtgggttg	ttggaaggac	ttacagaggt	gcagaatgta	13680
cgttgtacat	agcaggtttc	agcaaatggt	agctccctct	ttccccacat	ccattcaaat	13740
ctgttccttc	tccaaaggat	gtgtcaagga	ggaaatggac	ctggctggga	aacctcaga	13800
atactgggat	gatgctgagc	ttggctcata	cctgtgcttt	gctttcaggc	cagtacggaa	13860
ttcccaggcc	ctggatattt	ccttgcacca	agtcctactg	gtttggcgag	gaaagtgatg	13920
agaagagcca	ccctgggtcc	aaccagaaga	gaatgtcaga	aagtaagtgc	tgttgacctc	13980
ctgctctttc	tttaacctag	tgctgctgcc	tctgctaact	gttgggggca	agcgatgtct	14040
cctgcctttc	taaaagactg	tgaaaccact	ccaggggcag	agaaatcaca	tgagtggtcc	14100
ctttccaaat	cctcccatgc	catttatgtc	caatgctggt	gacctattgg	gagttcacgg	14160
tctcgatccc	tgagggacat	tttctttggt	gtcttggctt	ctagaagagt	atcttttact	14220
tgccccctcc	caaacacaca	tttcatgggt	tcctaacaag	ctagaagaaa	gaggtaaaga	14280
caagcgtgat	tgtggaacca	tagcctcgct	gcctgcctgt	gacatgggtga	cctgtgtatc	14340
agcctgtgtg	ggctgagacc	aagtggctac	cacagagctc	agcctatgct	tcataatgta	14400
atcattaccc	agatccctaa	tcctctcttg	gctcttaact	gcagacagag	atgtccacag	14460
ctcatcaaa	gctctgcttc	tgggttcttt	gtgcttagag	tggcttccta	aatattta	14520
agggtccctt	tctgccagtc	tcttctgtgc	ccatcccttg	attgcccttg	gtaaaagtat	14580
gatgcccctt	agtgtagcac	gcttgccctgc	tgttccta	catcttctcc	tacctctct	14640
ttacacctag	ctcctgtttc	agtcacctag	aaatgctcac	agtcgctgga	atatgtcatg	14700
ttcttccaca	cctccatgcc	tttgtaggta	ctgtttgctc	tcacaggaga	actttctctc	14760
taacttgcct	atcttctcaa	ctcctctctt	ctctccaga	tctagttccg	gateccctcc	14820
cctgagcatc	cctccttggg	tctcaggtag	tcagtcactc	tctgccctga	acttccatgg	14880
cacgtgaaag	aaaatctttt	tatttttaaa	caattacaga	ctcacaagaa	gtaatacaaa	14940

ttacatgagg	gggttccctt	aaacctttca	tccagtttcc	ccaatggtag	cagcatgtgt	15000
aactgtagaa	tagtatcaaa	accatgaaat	tgacataggt	acaattcaca	aaccttcttc	15060
agatttcact	agctttatgt	gcgctcattt	gtgtgtgtgt	gtgcgtattt	agttctatgc	15120
aattttatca	tgtgtgaatt	catgtaatta	ctagctcagt	caagctgcag	aaatatctca	15180
ttgtcacaaa	gctccttcct	gctacccctt	aatggccaca	gccacctccc	ttcttccctca	15240
gttccctgaca	cctgtcaacc	actaatgcgt	tcctcgtttt	tacagtttta	ttatttctag	15300
aatgtttacat	aaatggaacc	atacagtagg	tatccttttg	atactggcct	tttttttttt	15360
ttcactcagc	agtattccct	tagatctatc	caagttgtgt	gtgtcaacag	ttcattccctc	15420
ttcactgctg	agtagtggtc	cctgggaggg	gtgtatcaca	gttccatggc	attttttagat	15480
gtatttttta	aacagctttc	agcatcctct	atttttaattg	ttcatcaagt	cctttttccc	15540
aatagactct	gaatgctcct	ttatcatcgt	attcccatca	ccaacatcag	tacccaaata	15600
ggccctaaat	aaacattttat	agcctcctgc	ctgcctgaga	aaccaggggtg	gacatggaga	15660
gaaggcactt	ctgaaagtcc	aagcgcagtg	csctgtgtcc	ttacactcca	ctcctcagtg	15720
ctttctgtgg	gttcattttct	gtctttctctc	ctgtcacagt	ctgcatggag	gaggaaccca	15780
cccacttgaa	gctgggcgtg	tccattcaga	acctggtaaa	agtctaccga	gatgggatga	15840
aggtggctgt	cgatggcctg	gcactgaatt	tttatgaggg	ccagatcacc	tccttccctgg	15900
gccacaattg	agcggggaag	acgaccacca	tgtaagaaga	gggtgtgggt	cccgagaat	15960
cagccacagg	agggttctgc	agtagagtta	gaaatttata	ccttaggaaa	catgtctgat	16020
ccctggggcca	aggggaaggag	cacatgagga	gttgccgaat	gtgaacatgt	tatctaatca	16080
tgagtgtctt	tccacgtgct	agtttgctag	atgttatctt	ttcagcctaa	aacaagctgg	16140
ggcctcagat	gacctttccc	atgtagtcca	cagaattctg	cagtggctct	ggaacctgca	16200
gccacgaaaa	gatagattac	atatgttgga	gggagttggg	aattcccagg	aactctgtct	16260
ctaagcagat	gtgagaagca	cctgtgagac	gcaatcaagc	tgggcagctg	gcttgattgc	16320
cttccctgcg	acctcaagga	ccttacagtg	ggtagtatca	ggaggggtca	ggggctgtaa	16380
agcaccagcg	ttagcctcag	tggcttccag	cacgattcct	caaccattct	aaccattcca	16440
aagggtatat	ctttgggggg	tgacattctt	ttcctgtttt	ctttttaatc	tttttttaaa	16500
acatagaatt	aatatattat	gagcttttca	gaagattttt	aaaaggcagt	cagaaatcct	16560
actacctaac	acaaaaattg	tttttatctt	tgaataatat	gttcttggtt	gtccattttc	16620
catgcatgcg	atgttaggca	tacaaaatac	attttttaaa	gaatactttc	attgcaaatt	16680
ggaaacttcg	tttaaaaaat	gctcatacta	aaattggcat	ttctaaccga	tagggccact	16740
tgtagttatt	taccgaagca	aaaggacagc	tttgctttgt	gtgggtctgg	taggggtcat	16800
tagaaaggaa	tgggggcggg	gggaggggtg	gtgttctggt	ctctctgcag	actgaatgga	16860
gcatctagag	ttaagggtag	gtcaaccctg	acttctgtac	ttctaaattt	ttgtcctcag	16920
gtcaatcctg	accgggttgt	tccccccgac	ctcgggcacc	gcctacatcc	tgggaaaaga	16980
cattcgctct	gagatgagca	ccatccggca	gaacctgggg	gtctgtcccc	agcataacgt	17040
gctgtttgac	atgtgagtac	cagcagcacg	ttaagaatag	gccttttctg	gatgtgtgtg	17100
tgctatgcca	tcattggagg	agtgggactt	aagcatttta	ctttgctgtg	tttttgtttt	17160
ttcttttttt	cttttttatt	tttttgagat	ggagtctcgc	tctgtagcca	ggctggactg	17220
tagtggcgcg	atctcggtct	actgcaacct	tggcctccca	ggttcaagcg	attctcctgc	17280
ctcagcctcc	cgagttagctg	ggactctagg	cacacaccac	catgccagc	taatttttgt	17340
gttttttagta	gagacggggg	ttcaccatgt	tggccaggat	ggtctcaatg	tcttgacctc	17400
gtgatccgcc	cacctcggtc	tcccaaagtg	ctgggaacac	aggcatgagc	cactgtgtct	17460
ggccacattt	tactttcttt	gaatatggca	ggctcacctc	cgtgaacacc	ttgagacctc	17520
gttggttctt	gatttttagga	gaagtgggag	gtgaatgggt	gagctgtaga	ggtgacatca	17580
gcccagccag	tggatggggg	cttgggaaac	attgcttccc	attattgtca	tgctggaggg	17640
cccttttagcc	catcctctcc	ccccgccacc	ctccttattg	aggcctggag	cagacttccc	17700
agacctggta	gtgcttcagg	gccctgggat	gatggacctc	tatttgctgc	ttaagacatt	17760
tgctcccact	caggttgtcc	catcagccat	aaggccccca	gggagcccg	gtgatggagc	17820
agagagagac	ctgagctctg	caatcttggg	caaggctttt	cccttatggt	tcttcttatc	17880
taaagtgaac	agctggggct	catgtgctcc	ctcctcatct	aaagtgaaca	catggggctc	17940
atgtgcaggg	tcctccccgc	tttcagagcc	tgagggtccc	tgaggctcag	gaaggctgct	18000
ccagggtgagt	gccgagctga	cttcttggtg	gacgtgctgt	ggggacagcc	cattaaagac	18060
cacatcttgg	ggccctgaaa	ttgaaagtgt	taactgcctg	gtgcatgggt	gccaggcctg	18120
ctggaaacag	gttggaagcg	atctgtcacc	tttcactttg	atttcctgag	cagctcatgt	18180
ggttgctcac	tgttgttcta	ccttgaatct	tgaagattat	ttttcagaaa	ttgataaagt	18240

tatttttaaaa	agcacgggga	gagaaaaata	tgccattct	catctgttct	gggccagggg	18300
acactgtatt	ctgggggtatc	cagtagggcc	cagagctgac	ctgcctccct	gtccccaggc	18360
tgactgtcga	agaacacatc	tggttctatg	cccgttgaa	agggtctct	gagaagcacg	18420
tgaaggcga	gatggagcag	atggccctgg	atgttggtt	gccatcaagc	aagctgaaaa	18480
gcaaaaacaag	ccagctgtca	gggtcggccc	agagctacct	tccctatccc	tctcccctcc	18540
tcctccggct	acacacatgc	ggaggaaaat	cagcactgcc	ccagggtccc	aggctgggtg	18600
cggttggtaa	cagaaacttg	tccctggctg	tgcccctagg	tcctctgct	tcactcactg	18660
tctggggctg	gtcctggagt	ttgtcttgct	ctgttttttt	gtagggtgaa	atgacagaaa	18720
gctatctgtg	gccttggcct	ttgtcggggg	atctaagggt	gtcattctgg	atgaaccac	18780
agctgggtg	gacccttact	cccgcagggg	aatatgggag	ctgctgctga	aataccgaca	18840
agggtgcctga	tgtgtattta	ttctgagtaa	atggactgag	agagagcggg	gggcttttga	18900
gaagtgtggc	tgtatctcat	ggctaggctt	ctgtgaagcc	atgggatact	cttctgttak	18960
cacagaagag	ataaagggca	ttgagactga	gattcctgag	aggagatgct	gtgtctttat	19020
tcactctttt	gtccccaca	tggtgcacta	aatttatggt	tagttgaaag	gggtggatgct	19080
taaataaatg	gaagcggaga	ggggcaggaa	gacgattggg	ctctctgggt	agagatctga	19140
tgtggtacag	tatgaggagc	acaggcaggc	ttggagccaa	ctctggcttg	gccctgagac	19200
attgggaaag	tcacaacttg	cctcaccttc	tttgccgata	ataatagtgg	tgcgttacct	19260
catagaggat	taaatataat	gagaatgcac	acaaaccacc	tagcacaatg	cctggcatat	19320
agcaagtcc	caaataaaat	gcgtactggt	cttacctctg	tgaggatgtg	gtacctatat	19380
atacaaagct	ttgccattct	aggggtcata	gccatacagg	gtgaaagggt	gcttccaggt	19440
ctcttccagt	gcttaccct	gctaataatct	ctctagtccc	tgctactgtg	acaaatcaga	19500
actgagaggc	ctcacctgtc	ccacatcctt	gtgtttgtgc	ctggcaggcc	gcaccattat	19560
tctctctaca	caccacatgg	atgaagcggg	cgtcctgggg	gacaggattg	ccatcatctc	19620
ccatgggaag	ctgtgctgtg	tgggctcctc	cctgtttctg	aagaaccagc	tgggaacagg	19680
ctactacctg	accttggtca	agaaagatgt	ggaatcctcc	ctcagttcct	gcagaaacag	19740
tagtagcact	gtgtcatacc	tgaaaaagggt	gagctgcagt	cttggagctg	ggctgggtgtt	19800
gggtctgggc	agccaggact	tgctggctgt	gaatgatttc	tccatctcca	ccccttttgc	19860
catgttgaaa	ccaccatctc	cctgctctgt	tgcccctttg	aaatcatatc	atacttaagg	19920
catggaaagc	taaggggccc	tctgctccca	ttgtgctagt	tctgttgaat	ccggttttcc	19980
ttttcctatg	aggcacanag	agtgatggag	aaggctcctta	gaggacatta	ttatgtcaaa	20040
gaaaagagac	ttgtcaagag	gtaagagcct	tggctacaaa	tgacctgggc	gttctgtctc	20100
attacttttc	aatctcattg	accttaactt	ttaaaactata	aaacagccaa	tattttattag	20160
gcactgattt	catgccagag	acactctggg	cattgaaaga	aagtaatgat	aatagttaat	20220
tttatatagc	gttggttacca	tttcaacctt	tttttttttt	taacctctat	catctcaatt	20280
aaag						20284

<210> 22

<211> 7052

<212> DNA

<213> Homo sapiens

<400> 22

gtgaacacac	attaaagcat	gagaagcatg	aactagacat	gtagccaggt	aaaggccttg	60
ctgagatggt	tggcaaaggc	ctcattgcag	cattcattgg	caggccacag	ttcttttggc	120
agctctgctt	cctgaccttt	caccctcagg	aagcgaggct	gttcacacgg	cacacacatg	180
ccagacaggg	tccctctgaag	ccacggctgc	cagtgcattg	gtcccaggga	aagctttttc	240
ctttagttct	cacacaacag	agcttcttgg	aagccctccc	cggcgaagggt	gctgggtggct	300
ctgccttgct	ccgtccctga	cccgttctca	cctccttctt	tgccatcagg	aggacagtgt	360
ttctcagagc	agttctgatg	ctggcctggg	cagcgaccat	gagagtgaca	cgtgaccat	420
cggtaaggac	tctgggggtt	cttattcagg	tgggtgcctga	gcttccccca	gctgggcaga	480
gtggaggcag	aggaggagag	gtgcagaggc	tggtggcgtg	gactcaagggt	ttgtgtctgg	540
gctggggctg	gggtggctgcg	gggggtgggag	cagcttgggtg	gcgggttggc	ctaagtcttg	600
ctgggggtgcc	tggggctcgg	tttgggagct	agcagggcag	tgtcccagag	agctgagatg	660

attgggggttt	ggggaatccc	ttaggggagt	ggacactgaa	taccagggat	gaggagctga	720
ggggccaagcc	aggagggtgg	gattttgagct	tagtacataa	gaagagtga	agcccaggag	780
atgaggaaca	gccttccaga	tttttcttgg	gtagcgtgtg	taggaggcca	gtgtcaccag	840
tagcatatgt	ggaacagaag	tcttgaccct	tgctatctct	gcctagtcct	aatggctggc	900
ttttccagg	aaggcttctg	cttccatgga	ctgttagatt	aaccctttat	ttaggtaaat	960
gagggaaacct	actttataag	cataggaaa	ggtgaagaat	cttttaagat	tcctttactc	1020
aagttttctt	ttgaagaatc	ccagagctta	ggcaatagac	accagacttt	gagcctcagt	1080
tatccattca	cccatccacc	caccacacca	cccatccttc	catcctccca	tcctccatt	1140
cacccatcca	cccatccagc	tgtccaccca	ttctacactg	agtacctata	atgtgcctgg	1200
ctttgggtgat	acaaaggtga	ataagacata	gtcctttcct	ttgccccaa	ccctcagacc	1260
agagatgaac	atgtggaatg	acctaaacac	ctggaacagg	tgtgggtgat	gagcggcagg	1320
cctctgatga	gaggggtggg	gatggccagc	cctcactccg	aagccctctc	gagttgattg	1380
agccatcttt	gcattctggt	cctgcagatg	tctctgctat	ctccaacctc	atcaggaagc	1440
atgtgtctga	agcccggctg	gtggaagaca	tagggcatga	gctgacctat	gtgctgccat	1500
atgaagctgc	taaggaggga	gcctttgtgg	aactctttca	tgagattgat	gaccggctct	1560
cagacctggg	catttctagt	tatggcatct	cagagacgac	cctggaagaa	gtaagttaag	1620
tggctgactg	tcggaatata	tagcaaggcc	aaatgtccta	aggccagacc	agtagcctgc	1680
attggggagca	ggattatcat	ggagttagtc	attgagtttt	taggtcatcg	acatctgatt	1740
aatgttggcc	ccagtgaacc	atttaagatg	gtagtgggag	atagcaggaa	agaagtgttt	1800
tcctctgtac	cacagtacat	gcctgagatt	tgtgtgttga	aaccagtggg	acctaacaca	1860
tttacatccc	aaccttaaac	tcctatgcac	ttatttaccc	tttaatgagc	ctctttactt	1920
aagtacagtg	kgaggaacag	cggcatcagg	atcacttggg	aacttgtag	aaattcagca	1980
acttgggccc	agctcagacc	tactgaatca	gaatcaggag	caattctctg	gtgtgactgt	2040
gtcacagcca	ggtatcaact	ggattctcat	acatagggaa	tgacaaacgt	ttatggatgg	2100
atagtctact	tgtgccaggt	gctgagattt	gttttttgtt	ttttgatttt	tttttaataca	2160
ctgtgacctc	atttaattct	caaaaaaaga	tgaaaaaatg	aacactcagg	aatgctgaca	2220
tgagattcag	aatcaggggt	ttggggcttc	aaagtccatc	ctctctttat	ccatgtaatg	2280
cctcccttta	gagatacaac	atcacagacc	ttgaaggctg	aaggggatat	aaaagctgtc	2340
tggccaagtg	gtctccaagc	ttgacagtgc	agcagaatca	cctggggata	ttattaaapaa	2400
taaacatact	aaggtttggc	ttcagggcct	gtgaatcaga	atttctggag	gtgaggcctt	2460
gaagtctgta	tttctattgc	atacttttga	cacagtgggc	tatagactag	agtttggaaa	2520
tgattgcgct	cattcagatt	ctcttctgat	gtttgaattg	ctgccatcat	atttctagt	2580
ctctatttcc	tcctgtctcat	tctgtcttgg	ataacttatc	atagtactag	cctactcaaa	2640
gatttagagc	cacagtcctg	aaagaagcca	cttgactcat	tcctgtagg	ttcagaataa	2700
atttcttctg	cgcagtgtct	gtcatagctt	tttttaaat	tttttttatt	tttgatgaga	2760
ctggagtttt	gctcttattg	cccaagctgg	agtgcagtgg	tgcgattttg	gctcactgca	2820
acctccacct	cccaggttca	agcgattctc	ctgcctcagc	ctcccaagta	gctgagatta	2880
caagcatgtg	ctaccacgcc	cagctaattt	tgtattttta	gtagagatgg	gttttatcca	2940
tgttgggtcag	gctgggtctg	agctccagac	ctcaggtgat	ctgcccgcct	cggcctccca	3000
aagtgtctggg	attataggcc	tgagccacag	cgctcagcca	taactttaat	ttgaaaatga	3060
ttgtctagct	tgatagctct	caccactgag	gaaatgttct	ctggcaaaaa	cggcttctct	3120
cccaggtaac	tctgagaaag	tgttattaag	aaatgtggct	tctactttct	ctgtcttacg	3180
gggctaacat	gccactcagt	aatataataa	tcgtggcagt	ggtgactact	ctcgtaatgt	3240
tgggtgcttat	aatgttctca	tctctctcat	tttccagata	ttcctcaagg	tggccgaaga	3300
gagtgggggtg	gatgctgaga	cctcaggtaa	ctgccttgag	ggagaatggc	acacttaaga	3360
tagtgccctc	tgtctggctt	ctcagtgcac	gagtattgtt	cctttccctt	tgaattgttc	3420
tattgcattc	tcattttag	agtgtagggt	tgttgcagat	ggggaagggt	tgttttgttg	3480
taaataaaat	aaagtatggg	attctttcct	tgtgccttca	gatggtagct	tgccagcaag	3540
acgaaacagg	cgggccttcg	gggacaagca	gagctgtctt	cgcccgttca	ctgaagatga	3600
tgctgctgat	ccaaatgatt	ctgacataga	cccaggctctg	ttagggcaag	atcaaacagt	3660
gtcctactgt	ttgaatgtga	aattctctct	catgctctca	cctgttttct	ttggatggcc	3720
tttagccaag	gtgatagatc	cctacagagt	caaagagaa	gtgaggaaat	ggtaaaagcc	3780
acttgttctt	tgcagcatcg	tgcagtgtgat	caaacctgaa	agagcctatc	catatcactt	3840
cctttaaaga	cataaagatg	gtgcctcaat	cctctgaacc	catgtattta	ttatcttttc	3900
tgcgggggtcc	tagtttcttg	tatacatag	gtgtttaatt	gttgaacaaa	tattcattcg	3960

agtagatgag	tgatttttgaa	agagtcagaa	aggggaattt	gctgttagag	ttaattgtac	4020
cctaagactt	agatatattga	ggctgggcat	ggtaggtcat	gccagtaatc	ccagcgcttt	4080
gagaggctga	ggtaggtaga	tcacctgagg	tcaggagttt	gagaccagtc	tgaccaacaa	4140
ggtagaaacc	cgtctctact	aaatacaaaa	aattagccga	gtgtgggtggc	acatgcctgt	4200
catcccagct	acttgggagg	ctgaggcagg	agaatcgctt	gaacccagga	ggcagagggt	4260
gcagtcagcc	acgggtgcgc	cattgcactc	cagactgggc	aacaagagtg	aaaactccat	4320
ctcaaaaaag	aaaaaaaaaag	aattagatat	tttggatgag	tgtgtctttg	tgtgtttaac	4380
tgagatggag	aggagagcta	agacatcaaa	caaataattgt	taagatgtaa	aagcacatca	4440
gttaggtatc	attagtttag	gacaaggatt	tctagaaaat	ttttagggaac	agaaaaacttt	4500
ccagttctct	cacccttgct	caaagagtg	atggctctta	cattatata	aactgcctga	4560
cttcatacag	tatcagtact	tagatcattt	gaaatgtgtc	cacgtttttac	caaatataa	4620
taggggtgaga	agctgagatg	ctaattgcca	ttgtgtattc	tcaaataatgt	caagctacgt	4680
acatggcctg	tttcatagag	tagtctataa	gaaattgatg	acttgattca	tccgaatggc	4740
tggtgtaac	acctgggttac	gcataaacac	ctcttttcag	ttgtctcaag	acacctttct	4800
tttctgtact	tatcagacaa	ggactgaaag	gcagagactg	ctactgttag	acattttgag	4860
tcaagctttt	ccttggacat	agctttgtca	tgaaagccct	ttacttctga	gaaacttcta	4920
gcttcagaca	catgccttca	agatagttgt	tgaagacacc	agaagaagga	gcatggcaat	4980
gccgaaaaca	cctaagataa	taggtgacct	tcagtgttgg	cttcttgcag	aatccagaga	5040
gacagacttg	ctcagtggga	tggatggcaa	agggtcctac	caggtgaaag	gctggaaact	5100
tacacagcaa	cagtttgtgg	cccttttgtg	gaagagactg	ctaattgcca	gacggagtctg	5160
gaaaggattt	tttgcctcagg	tgagacgtgc	tgttttcgcc	agagactctg	gcttcattggg	5220
tgggctgcag	gctctgtgac	cagtgaaggc	aggatagcat	cctgggtcaag	atatggatgc	5280
cggagccaga	tttatctgta	tttcaatccc	agttctattc	cttgccagtt	gtgtatccgc	5340
tggcaagtta	cttctctatg	cctcaatctc	ctcatctgta	aaatggggat	aataatatta	5400
cctgcaatac	aggggtgtta	cgaaaataaa	aatgaatagg	tgcttagaat	ggggcctgac	5460
attagtaagt	gcttagtttt	gtgtgtgtat	atgttatttt	tattttggag	gagaacataa	5520
aaaggacaaa	gtgtagaaaa	actgggtggg	tgtattcagc	tgtcataaca	tgagagttgt	5580
tatgccaga	tgacttgac	atgtgaattt	attagaaaca	tgatttttct	ctgagttgat	5640
gtttaactca	aactgataga	aaagataggt	cagaatatag	ttggccaaca	gagaagactt	5700
gttagactat	tgtctgcatg	tcagtgtttg	catgctaact	tgcttagtta	gaaagggttaa	5760
atTTTTTcac	tctataaaat	caagaaatat	agagaaaagg	tctgcagaga	gtctttcatt	5820
tgatgatgtg	gatattgtta	agagcgggag	tttggagcat	acagagctca	agttgaatcc	5880
tgactttgct	acttattggc	tatatgacct	tgggcaagct	gcttagtctc	tctgatcctc	5940
agttaccttt	gtttgttgat	gatgaccatt	gataacacaa	ccataaataa	tgacaacata	6000
gagatagttc	tcattatagt	agttgttata	cagaattatt	cactcaatgt	taattttctg	6060
cattgaaatc	ccagaacatt	agaattgggg	gcattatttg	aatctttaag	gttataagga	6120
atacatttct	cagcaataaa	tggaaggagt	tttgggttaa	cttataaagt	atacccaagt	6180
catttttttt	cagagaagat	atggtagaaa	gtcttaggag	gttgaagaag	gaattggata	6240
tttattcttt	ctgagactat	catgggagat	aatgactatg	gttgtccatg	attggagccg	6300
ttgctgtaga	gttgggttta	ttatagtgtg	ggatttgaat	gggccatgtg	ttctcagacc	6360
tcagaataaa	aagagaaaac	tgaggccagt	ggggagcgtg	acttcacatg	ggtagacttg	6420
tgctagagac	agaaccagga	ttcaggactt	ctggctcctg	gtcctgggtt	catggcccaa	6480
tgtagtcttt	ctcagtcttc	aggaggagga	agggcaggac	ccagtgttct	gagtcaccct	6540
gaatgtgagc	actattttact	tcgtgaactt	cttggcttag	tgctctgccc	aggtggccat	6600
aacctctggc	cttgtgttgc	cagagaaaaag	gttttagttt	caggctccat	tgcttcccag	6660
ctgccaagaa	tgccctgggtg	cagcacagtc	ataggccctg	cattcctcat	tgccgtgctg	6720
gttgggtcggg	gaggtgggct	ggactcgtag	ggatttgccc	cttggccttg	tttctaacac	6780
ttgccgtttc	ctgctgtccc	cctgccccct	ccactgcctg	ggtaaagatt	gtcttgccag	6840
ctgtgtttgt	ctgcattgcc	cttgtgttca	gcctgatcgt	gccacccttt	ggcaagtacc	6900
ccagcctgga	acttcagccc	tggatgtaca	acgaacagta	cacatttgtc	aggtatgttt	6960
gtcttctaca	tcccaggagg	gggtaagatt	cgagcagacc	aaagatgttt	acgagggcca	7020
agggaaatgga	cttcagaatt	acacggtgga	at			7052

<210> 23
 <211> 2534
 <212> DNA
 <213> Homo sapiens

<400> 23
 gggaagcatt taaaaaaaaa aaagtatata tatatatata tatatatata tgtaatgtga 60
 attggcctct ttttctctaa gccacattt tcttcttaca tagttcaggt ttactttatt 120
 ttttcctttc cggctgctga cctgtattg cccgtagttg tggaacatag catgtgtttg 180
 tgacctgtgc ctgttatttt tgtgctttct agttgtgcat gcaaagagta caaagttttc 240
 ttgccctttc ttggaaaatc ctgcttgtct gtgccaaagg gataattgtg aaagcacttt 300
 tgaaatactt aatgagttga ttttcttcaa attaaaaaaaa atatatataat gtatatgtgt 360
 atgtacatgt gtgtacacat acacaccttt atacatacag ccattttaa acaagctcca 420
 ctttgaggag ctctacgtca cctgatgcc gaatacaggg ccagagtctg agatccttct 480
 ggggtggtttc tgtgttttgt tcatttctgt ttttaagagcc tgtcacagag aaatgcttcc 540
 taaaatgttt aatttataaa aacattttta tctctcgatt actggtttta atgaattact 600
 aagctggctg cctctcatgt acccacagca atgatgtcc tgaggacacg ggaaccctgg 660
 aactcttaaa cgccctcacc aaagaccctg gcttcgggac ccgctgtatg gaaggaaacc 720
 caatcccgtg agtgccactt tagccataag cagggcttct tgtgcttgtt gcctgggtttg 780
 atttctaata tgctgcattt atcaactgca tgccacattg tgaccgccag catttgccct 840
 ttgaattatt attatgtttt atttacaata agcgaaggta gtaaccgaac taaattatct 900
 aggaacaaac gtttgagag tcttctaaca ccgyscaaag cacgtcatta cagacatttg 960
 ttacttgatt tagaacctta atatttaatt taaatacgca ctttactct actgatgaaa 1020
 tgcttttctt tcttttctct cccagccctt gtacttaagt gcttcaatag gctctcatta 1080
 tatatgattt ttaggttttg cttatcagct tcttcgcttt tataatctga aaagatggca 1140
 tatgaatttt tataaaaagg gacactttct tcttctcaaa ttgtatatatt ttattgtact 1200
 ttcttcaaa accccctttt aaaaagtaag cagtggataa ataaattcag tgaagcatcc 1260
 atatgacctt taagttagtg taggggaagg gaggtcacca gatcactgtg agtgaagatg 1320
 gtggagaggt gaggatctta tgaggccgtg ctcaaggctg gtagagggtg gtagtggttt 1380
 ccagggttag gcagaatctc agctgaggtc atgaaacaac agtgatctct gaaaaattat 1440
 ggcaagggtg gaagggtgctg gagaattgga gagggggcaa acttgacttt caagtttcaa 1500
 tgggaagata ggtgactctg cacaccacag aacagtgagc atgataacct gtttatacaa 1560
 ggttctagag cagatttcta aatggatagc tactgtgtgc ttgtttgttc ttaattagta 1620
 ttggatagtt actaaatact tgttagtact tagtacataa tgggtggtaa atcctagcag 1680
 ctaatatttg ttcccaata accagatgac aaggatagag aaggacacag acacggccta 1740
 tctggatttc atggtgcctt tgattttcca catgaagggt gtgtagggaa gatagaagca 1800
 tgagatgaga tgataatata gttatctgga ttcactactg gccagctgaa ccatatgaac 1860
 tcatggattg atgctagctt aggaaggctc tgtaggagcc agaactgggc tgagagccag 1920
 cccatagaga caaaagaggg ccggccctga catcagaggg ttcaaactg atgtctgagc 1980
 cccacctaca gtctgccgga ggtgggttga aggaagagcc tttatcctta caaataattac 2040
 tgaaattcaa attttttaggt tttgcaaaaa aatgggtggc ctgaaggaaa tttgacagga 2100
 gcatgtctca gctgtattta aatttgtctc agccaatccc cttttgaatg ttcagagtgt 2160
 aagcttcagg agggcagcgc gtcttagtgt gacttttctg gtcagttcag gtgctttaag 2220
 gagacaatta gagatcaatc tggaaaactt catttgaatt tttatacat aagaaaacaa 2280
 taagaaatag ttaaaaaatat atatttatat aatatatata tgtgtgtgtg tgtgtgtgtg 2340
 tgtgtgtgtg tatatatata tatattttat ttattttatt ttttttgaga tggagtctcg 2400
 ctctgttgcc caggctggag tgcagtggct caatcttggc tcaactgccac ctctgcctcc 2460
 caggttcaag tgattctcct acctcagcct cctgagtagc tgggattaca agcatgtgcc 2520
 accacactgg cttaa 2534

<210> 24
 <211> 2841
 <212> DNA
 <213> Homo sapiens

<400> 24

tcttgccagt	ctctactcat	ttttcagcac	atcgagcata	agatccagac	tctttcccag	60
gcctctctca	tctggctcct	ctcctcctcc	tttatcatta	ctcttcttcg	tagcttatcc	120
tactccagcc	atgctgtctt	cctattatcc	ctaaaaarta	gaaatgcatt	tcttcctagg	180
gcctttgtac	ctgcacttgc	catcgctttt	gctcagaatg	ttctttttgc	caagcttttg	240
cccagcttgt	tctccatcat	tgttatgttt	tggctgaaat	gtcttctctt	agtaggttca	300
ttctccccag	tactgtctt	tttattttgc	tttattttgg	gccatcttaag	gttatcttat	360
tagtgatatt	gttggtcgtc	tcctccatgg	gcatacacct	ccatgaaggc	aggatatttt	420
accttaggcc	ctcgaatata	ctggacagca	tctggcacgt	agtagatgct	caacgaatgt	480
ttgttggtg	agcaaagtgt	tgggtgattg	gattgaactg	agttcagtat	gtaaatattt	540
agggcctctt	tgcattctat	tttacttatg	tataaaatga	tacataatga	tgatataaat	600
gatgtcacag	tgtacaaggc	tgttggtgga	tcaagcaatc	aaatgagatc	atgcttgtct	660
tttccaaatg	gtgagggaat	agatgcatgt	ttgtgggtgt	tacgggaatga	tctgtgtctc	720
ctgaggcaac	agaaaggcca	ggccatctct	ggtaatccta	ctcttgctgt	cttccctttg	780
cagagacacg	ccctgccagg	caggggagga	agagtggacc	actgccccag	ttccccagac	840
catcatggac	ctcttccaga	atgggaactg	gacaatgcag	aacccttcac	ctgcatgcc	900
gtgtagcagc	gacaaaatca	agaagatgct	gcctgtgtgt	ccccagggg	caggggggct	960
gcctcctcca	caagtgaagc	actttcaggg	gggtgattggg	cagaaggggg	gcaggatggg	1020
ctggtagctt	ccgcttgga	gcaggaatga	gtgagatata	atgttgggag	ggctgttttc	1080
agtctttttt	gttttttgtt	tttttttctg	aggcggagtc	ttgctctgtc	gccaggctg	1140
gagtgtgtg	gcatgatctt	gcctcactgc	aacctccacc	tcccagggtt	aagcgattct	1200
cctgcctcag	cctcctgagt	agctgggatt	acaggcacgc	accaccatgt	ctggctaatt	1260
tttgtgtttt	tagtagagat	aggggtttcg	cgtgttggtc	aggctgggtc	ggaattcctg	1320
acctcaggtg	atccaccctg	ctcgccctcc	caaagtgtct	ggattacagg	cgtgagccac	1380
tacgcccagc	cctgtttcag	tctttaactc	gcttcttgtc	ataagaaaaa	gcatgtgagt	1440
tttgagggga	gaagggttgg	accacactgt	gcccattgct	gtcccacagc	agtaaagtca	1500
caggacagac	tgtggcaggc	ctggcttcca	atcttggctc	tgcaacaaat	gagctggtag	1560
cctttgacag	gcctgggctt	gtttcttcc	ctctgaaatg	gggaggctgg	accagaaaac	1620
tctgtgggat	cttgtcaact	ctggattctt	tagagactct	gtttgggaag	gagtcctgag	1680
ccattttttt	tttcttgaga	atttcaggaa	gaggagtgtc	tatgatagct	ctctgctgct	1740
tttatcagca	accaaattgc	aggatgagga	caagcaattc	taaatgagta	cagggaactaa	1800
aagaaggctt	ggttaccact	cttgaaaata	atagctagtc	cagggtgcggg	gtggctcaca	1860
cctgtaattc	cagtattttg	ggatgccgag	gtggactgat	cacctaaagg	caggagtctg	1920
aaaccagctt	ggccaatgtg	gcgaaaccct	gtctctacta	aaaattcaaa	aattagccag	1980
gcatggtggc	acatgcctgt	aatcccagtt	acttgggagg	ctgaagcagg	agaattgctt	2040
gaacctggga	ggtggaggtc	gcagggagcc	aaaattgcgc	cactgtactc	cagcctgagc	2100
aacacagcaa	aactccatat	caaaaaataa	aatgaataaa	ataacagcta	atctagtc	2160
cagtataaact	ccagtgaaca	gaagatttat	taggcatagt	gaatgatggt	gcttcctaaa	2220
aatctcttga	ctacaaagaa	tctcatttca	atgtttattg	tttagatgtt	cagaataaat	2280
tcttgggaaa	gaccttggct	tgggtgaagt	gaattaccag	tgccgagggc	agggtgaacc	2340
aagtctcagt	gctgggtgac	tgagggcagt	gtctgggacc	tgtagtcagg	tttccggtca	2400
cactgtggac	atggctcactg	ttgtccttga	tttgttttct	gtttcaattc	ttgtctataa	2460
agaccctgat	gcttgggtttt	catgtgatga	cagagaaaac	aaaacactgc	agatatcctt	2520
caggacctga	caggaagaaa	catttcggat	tatctggtga	agacgtatgt	gcagatcata	2580
gccaaaagg	gactttttac	taaacttggc	ccctgcctta	ttattactaa	ttagaggaat	2640
taaagacct	caaataacag	actgaaacag	tgggggaaat	gccagattat	ggcctgattc	2700
tgtctattgg	aagtttagga	tattatccca	aactagaaaa	gatgacgaga	gggactgtga	2760
acattcagtt	gtcagcttca	aggctgaggc	agcctggtct	agaatgaaaa	tagaaatgga	2820
ttcaacgtca	aattttgcc	c				2841

<210> 25

<211> 852

<212> DNA

<213> Homo sapiens

<400> 25

gcatgctgga	gtgatagtga	ccatgagttt	ctaagaaaga	agcataattt	ctccatatgt	60
catccacaat	tgaatatatta	ttgttaattg	aaaaagcttc	taggccaggc	acggtggctc	120
atgcctgtaa	tcccagcact	ttaggagcca	aggcgggtgg	atcacttgag	gtcaggagtt	180
tgagaccagc	ctggccaaca	tggggaaacc	ctgtctctac	taaaaatata	aaataagctg	240
ggcgtgggtg	tgcgtgcctg	taatcccagc	tacttgggag	gctgaggcag	gagaactgct	300
tgaatctggg	aggcggaggt	tgagtgagc	tgagttcatg	ccattgcatt	ccagcctggg	360
caacaagagc	gaaacccatct	cccaaaagaa	aaaaaaaaga	aagaaaaagc	ttctagtttg	420
gttacatctt	gggtctataag	gtggtttgta	aattggttta	acccaaggcc	tggttctcat	480
ataagtaata	gggtatttat	gatggagaga	aggctggaag	aggcctgaac	acaggcttct	540
tttctctagc	acaaccctac	aaggccagct	gattctaggg	ttatttctgt	ccgttctcta	600
tatcctcagg	tggatattta	ctccttttgc	atcattagga	ataggctcag	tgttttcttt	660
gaactgattt	tttgtttctt	tgtctctgca	gcttaaagaa	caagatctgg	gtgaatgagt	720
ttaggtaagt	tgctgtcttt	ctggcacgtt	tagctcaggg	ggaggatggg	gttgtagggtg	780
tgcttgaggt	gaagaaagcc	ttggggattg	tttgtcactc	acacacttgt	gggtgccatc	840
tcactgtgag	ga					852

<210> 26

<211> 6289

<212> DNA

<213> Homo sapiens

<400> 26

gctttataga	gtttctgcct	agagcatcat	ggctcagtgc	ccagcagccc	ctccagagggc	60
ctctgaatat	ttgatatact	gatttccttg	aggagaatca	gaaatctcct	gcagggtgtct	120
agggatttca	agtaagtagt	gttgtgaggg	gaatacctac	ttgtactttc	cccccaaacc	180
agattcccga	ggcttcttaa	ggactcaagg	acaatttcta	ggcatttagc	acgggactaa	240
aaaggctcta	gaggaaataa	gaagcgccaa	aaccatctct	ttgcactgta	tttcaaccct	300
tttgtccttc	tgggttttga	aggaacaggt	gggactgggg	acagaagagt	tcttgaagcc	360
agtttgtcca	tcatggaaaa	tgagataggt	gatgtggcta	cgtcaggggg	cccgaaggct	420
ccttggtact	gatttccgtc	ttttctctct	gccttttccc	caagggccag	gacccctgga	480
tctctgggca	gagcagacgc	aggcccctat	aatagccctc	atgctagaaa	ggagccggag	540
cctgtgtata	aggccagcgc	agcctactct	ggacagtgc	gggttcccac	tctcccaact	600
ccccatctgc	ttgcctccag	acccacattc	acacacgagc	cactgggttg	gaggagcatc	660
tgtgagatga	aacaccattc	tttcttcaat	gtctcagcta	tctaactgtg	tgtgtaatca	720
ggccagggtcc	tccctgctgg	gcagaaacca	tgggagttaa	gagattgcca	acatttatta	780
gaggaagctg	acgtgtaact	tctgaggcaa	aatttagccc	tcttttgaa	aggaatttga	840
ctcagtgaac	ctgtacaca	ctcgcactga	gtctgtgctg	gatgatactg	tgcacccac	900
tgtctgggtt	ttaatgtcag	gctgttcttt	taggtatggc	ggcttttccc	tgggtgtcag	960
taatactcaa	gcacttcctc	cgagtcaaga	agttaatgat	gccatcaaac	aatgaagaa	1020
acacctaaag	ctggccaagg	taaaatatct	atcgtaagat	gtatcagaaa	aatgggcatg	1080
tagctgctgg	gatataggag	tagttggcag	gttaaacgga	tcacctggca	gctcatttgt	1140
ctgaatatgt	tggcatacag	agccgtcttt	ggcatttagc	gattttgagcc	agacaaaact	1200
gaattactta	gttgtagctt	taaaagtgt	ggtcaaaaac	aaatccagag	gccaggagct	1260
gtggctcatg	cctgtaatcc	tagcactttg	ggaggctgaa	gcgggtggat	cacttgagggt	1320
caggagttcg	agaccagcct	ggcctacatg	acaaaacccc	gtatctacta	aaaatacaaa	1380
aaaattagct	gggcttggtg	gcacacacct	gtaatcccag	ctacttggga	ggctgaggca	1440
ggagaattgc	ttgaaccctg	taggaagagg	ttgtagttag	ccaagatcgc	accgttgac	1500
tccagcctgg	gcaacaagag	caaaactcca	tctcaaaaaa	caaattaaat	ccagagattt	1560
aaaagctctc	agaggctggg	cgcggtggct	tacacctgtt	atcccagcat	tttgggatgc	1620
cgaggcgggc	aaagcacaag	gtcaggaggt	tgagaccagg	ctggccaaca	tagtgaaacc	1680
ctgtctctgc	taaaaacata	gaaaaattag	ccgggcatgg	tggcgtgcgc	ctgtaatccc	1740
agctactcgg	gaggctgagg	tgagagaatt	rocttgaacc	gggaggcgga	gggtgcagtg	1800
agcccagatt	gcaccactgc	actccagcct	gggcgacaga	gcaagactcc	atctcaaaaa	1860
aagctctcag	aacaaccagg	tttacaatt	tgggtcagttg	gtaaataaac	tgggtttcaa	1920

acatacttttg	ctgaaayaat	cactgactaa	ataggaaatg	aatctttttt	tttttttttt	1980
taagctggca	agctggctcg	taggacctga	taagtactca	cttcattttct	ctgtgtctca	2040
ggtttcccat	ttttaggtga	gaattaaggg	gctctgataa	aacagaccct	aggattgtgg	2100
acagcagtga	tagtcctaga	gtccacaagt	ctgcttttga	gtgatgggcc	catgtatctg	2160
gcacatctgc	aggcagagcg	tggttctggc	tcttcagatg	atgccggtgg	agcactttga	2220
ggagtccctca	ccccaccgtg	ataaccagac	attaaaatct	tggggctttg	catcccagga	2280
tttctctgtg	attcctttcta	gacttgtggc	atcatggcag	catcactgct	gtagattttct	2340
agtcacttgg	ttctcaggag	cgttttattt	aatggcttca	catttaattt	cagtgaacaa	2400
ggtagtggca	ttgctcttca	cagggccgtc	ctgttgtcca	caggttccag	attgactggt	2460
gccccttatc	tatgtgaaca	gtcacaactg	aggcagggtt	ctgttgttta	caggacagtt	2520
ctgcagatcg	atttctcaac	agcttgggaa	gatttatgac	aggactggac	accagaaata	2580
atgtcaaggt	aaaccgctgt	ctttgtttcta	gtagcttttt	gatgaacaat	aatccttatg	2640
tttctggag	tactttcaac	tcattggtaaa	gttggcaggg	gcattcacaa	cagaaaagag	2700
caaaactatta	actttaccag	tgaggcagta	cgggtgtagt	tagtgattca	gagaatttgc	2760
tttgccacca	gacataccag	gtaaccttga	ctaagttact	taacctatct	aaacctcagt	2820
tycctcatct	gtgaaatgga	gacagtaatc	atagctattt	ccaaactggt	gtgagaattc	2880
aatgagttaa	aggtataagg	tcctcaccac	agcgctgcc	cacatagtca	gtgatcacta	2940
tgtcctgaac	actgtaatta	cttcgccata	ttctctgata	atagtgtttt	gccttggtat	3000
gtgactagaa	tttctttctg	aggtttatgg	gcatgggttg	tgggtatgca	cctgcctgca	3060
ggagcccggg	ttgggggcat	taccttgtac	ctgggtatgt	ttctttcagg	tgtggttcaa	3120
taacaagggc	tggcatgcaa	tcagctcttt	cctgaatgtc	atcaacaatg	ccattctccg	3180
ggccaacctg	caaaagggag	agaaccctag	ccattatgga	attactgctt	tcaatcatcc	3240
cctgaatctc	accaagcagc	agctctcaga	gggtggctctg	taagtgtggc	tgtgtctgta	3300
tagatggagt	ggggcaaggg	agaggggttat	ggagaagggg	agaaaaatgt	gaatctcatt	3360
gtaggggaac	agctgcagag	accgttatat	tatgataaat	ctggattgat	ccaggctctg	3420
ggcagaagtg	ataagtttac	gaattggctg	gttgggcttc	ttgaactgca	gaagagaaaa	3480
tgacactgat	atgtaaaaat	cgtaaccattt	agtgaattca	tataaagtga	gttcaaaaaa	3540
tgtaatttaa	attataattt	aattataagt	gtttaatcag	tttgatttgt	ttaaaaacca	3600
ctgtttttaa	tttgggtggaa	tatgttttta	ttagcttgta	tctttaattc	ctaaattaaag	3660
ctgtgtgtgt	gtgtgtgtgt	gtgtgtgtgt	gtgtgtgtgt	gtgtgtgtgt	gaagttttaa	3720
gccaggatga	gctagtttaa	agtatgcagc	ctttggagtc	atacagatct	gggtttgaat	3780
ctgggtctcta	aactttatag	atgtatgata	ttaaatgagg	cagttcatgt	aaattgcca	3840
gcccagcact	cagcacagag	ttgatatttc	acacacatta	gatacctttc	ctgtatgtgg	3900
agcatggcag	ttcctgtttc	tgctttactc	ctacaggata	ctaataatagg	acactaggat	3960
ctttatacca	agaccccatg	taatgggctt	atgagaccat	tcttcttata	aaaatctgac	4020
agaatttttg	tatgtgttag	atcaataggc	tgcatactgt	tattttcaag	ttgatttaca	4080
gccagaaata	ttaattttatt	tgagtgttta	cagagttaata	tttctgctct	catttagttt	4140
tcaagcccca	ctagtccttt	gtgtgtgtaa	atttacaact	tactgtctct	acaaggctat	4200
gaacagtggg	ccaaagtga	tgccattaac	cactctgact	tccttcatta	gttttattgt	4260
gacagtggac	tcttttgacc	tcagtaatac	cagtttgcca	tttacattgt	catattttta	4320
gacttaaaaa	tgatcatctt	aaccctgaat	aaaatgtgtc	tgggtgaacag	atgtttttcc	4380
ttggctgtgc	ctcagatatc	tctgtgtgtg	tgtacgtgtg	tgtttgtctg	tgtgtccatg	4440
tcctcactga	ttgagcccta	actgcatcaa	agaccctca	gattttcaca	cgctttttct	4500
ctccaggatg	accacatcag	tggatgtcct	tgtgtccatc	tgtgtcatct	ttgcaatgtc	4560
cttcgtccca	gccagctttg	tcgtattcct	gatccaggag	cgggtcagca	aagcaaaaca	4620
cctgcagttc	atcagtggag	tgaagcctgt	catctactgg	ctctctaatt	ttgtctggga	4680
tatggtaagg	acacaggcct	gctgtatctt	tctgatgtct	gtcagggccca	tggattgata	4740
tggataagaa	agaaagagct	ctggctatca	tcaggaaatg	ttccagctac	tctaaagatg	4800
tatgaaaaag	aaatagccag	aggcagggtga	tcactttcat	gacaccaaac	acagcattgg	4860
gtaccagagt	tcattgtcaca	ccagagggaa	aattctgtac	acaatgatga	aaattaatac	4920
cactaccact	taagttccta	tgtgacaact	ttcccaagaa	tcagagagat	acaagtcaaa	4980
actccaagtc	aatgcctcta	acttctctga	tgggttttaa	cctccagagt	cagaatgttc	5040
tttgcccttac	taggaaagcc	atctgtcatt	tagaaaaact	tgtacatttt	atcagcagct	5100
tatccatcca	ttgcaaata	tgtttttgtg	ccasccacaa	tatattgctt	ctatttggac	5160
caatatgggg	gatttgaagg	aattctgaag	ttctaattat	atttcaactc	tactttacaa	5220

tatctccctg	aaatatatct	ccctgtaact	tctattaatt	ataagctaca	cagagcaa	5280
ctaattcttc	ccccaccgaa	caagtcctcg	gatattttaa	aataactctc	atactctcat	5340
ttaacctgag	tattaccag	ataagatgat	atatgagaat	acaccttgta	acctccgaag	5400
cactgtacaa	atgtgagcaa	tgatggtgga	gatgatgatg	agatctttgc	tgtttataacc	5460
aagcccctta	gactgtgtca	ctctctgat	ccggttggtc	ttgtatggcc	atgctgtata	5520
ttgtgaatgt	cccgttttca	aaagcaaagc	caagaattaa	ccttggtgttc	aggctgtggt	5580
ctgaatggtt	atgggtccag	agggagtga	tctttagctc	acacttctat	tactgcagca	5640
caaagatttt	gcattttgga	aggagcaccg	tcttactggc	aacttagtgg	taaaccacaaa	5700
cctccatttc	acacaaatga	ttgtgaaatt	cgggtctcct	tcattctata	caaattcatt	5760
tgattttttt	gaaactaaac	tttatattta	tccatattaa	attacatggg	ttttattttt	5820
gttttatctt	gattcagtaa	ttactccttt	cagtaaacac	agactgagtg	ctgtgtgtct	5880
gacttatgcc	aggcataggt	gattcagaga	tgaaagggtca	agtccctgaa	cccattctctt	5940
gtcttccctg	gtattatctg	tccctccctg	ctttagagct	cctgaaattt	gctagaagca	6000
tgtcttcate	taagttgttg	ataaacacat	caagtaggat	tggactgagg	cagagccctg	6060
tagtctgaag	ctgcagttct	tctagcggct	gacaagcccc	actatcactt	ccctgctggt	6120
gctttgctct	gccagctgtg	aattctcata	attgtcctat	cgtcaagtct	ttatttctgc	6180
attttactgc	ttgatacact	gtcaggacag	actttaaaat	tattctcagt	gcgatgaaac	6240
aattctgaca	ttcatgttat	gagcagttac	ctcataaata	gattacatg		6289

<210> 27

<211> 4244

<212> DNA

<213> Homo sapiens

<400> 27

aaattactct	gactgggaat	ccatcgttca	gtaagtttac	tgagtgtgac	accttggtctt	60
gactgttgga	aagacagaaa	gggcatgtag	tttataaaat	cagccaaggg	gaaaatgctt	120
gtcaaaatgt	attgtcgggt	attttgatta	atagtttatg	tggcttcatt	aattcagagt	180
tactctccaa	tatgtttatc	tgccctttct	tgcttgataa	tggtgaaaac	ttgtgtgatg	240
cattgtatat	ttgatttagg	ggtgaactgg	atgtctttgt	tttcactttt	agtgcatta	300
cgttgtccct	gccacactgg	tcattatcat	cttcactctgc	ttccagcaga	agtcctatgt	360
gtcctccacc	aatctgcctg	tgctagccct	tctacttttg	ctgtatgggt	aagtcacctc	420
tgagtgaggg	agctgcacag	tggataaaggc	atttggtgcc	cagtgtcaga	aggagggcag	480
ggactctcag	tagacactta	tctttttgtg	tctcaacagg	tgggtcaatca	cacctctcat	540
gtacccagcc	tcctttgtgt	tcaagatccc	cagcacagcc	tatgtggtgc	tcaccagcgt	600
gaacctcttc	atggcatta	atggcagcgt	ggccaccttt	gtgctggagc	tgttcaccca	660
caatgtgagt	catgcagaga	gaacactcct	gctgggtaga	gcactctctg	gagccagagg	720
acagtgttta	attgtgatct	tattccactt	gtcagtggta	ttgacactgc	tgactgcctt	780
gtcctgtctt	cagagtctgt	cttccctgag	aaggcaaagc	acctttcttt	cttgctgtgc	840
cttacatttt	gctgggtcaag	cctttcagtt	tcttttgaca	gtttttttta	cttctttctt	900
ttttcaatgt	tgctcttacc	aagagtagct	cctctgcctt	ccactttaca	catgagagct	960
gggcgacgca	ttcagtccta	aggcttttac	catcacctct	cttggtgttt	ttattgtcat	1020
ctctaagatc	aatgccttta	gccttgatca	taaccttgaa	ctctaactctc	aaattctcac	1080
ttgcctagt	gattgtccca	tttagatagt	atatagatac	cccaacctgg	atatgtccta	1140
gttttctttc	cccttggaa	ttaatgcttt	tcttgccatc	cctgtcacac	tcagtggcac	1200
taccatccac	tcggttgccc	aagctggctc	ttagagttaa	cctagatgct	tgctttgtctg	1260
ttgcagat	cccacattca	actggttatg	ttgtcagttc	ttccaggtat	ggacctctaa	1320
aataaggctt	ccctccatt	ccggttggtc	ttgcctttgt	ccaaacacag	cacacaaggc	1380
cttttacagt	tgcacaactc	ttcctgtcca	taccacacc	accttttccc	agctgtaagc	1440
ttcagatgag	ttgcctccaa	ccaccatgct	cctgtaggcc	tggttgaaa	tgcccttctt	1500
ctgtcacagg	gtctggtagt	atatcccttg	cccttcaaga	tttagctaaa	atgtgaagct	1560
ttccttacct	gctgggaggt	gttctctctt	ttctctgtgc	tctcagagtc	cttagtccat	1620
gcctccagta	caacgtacat	ccacttacat	ggtaatttcc	tgtttacata	cttttctctac	1680

tcggagtgga	gtctgtttct	taataatfff	gcctctccca	tgccctagca	cagtgcaccc	1740
agcgtatagc	cccttattca	gttggttagat	atftggccac	tgttgccctg	tgggatcata	1800
agttctgatg	tatttgagaa	gaatftctaa	aattctgaca	aaatcctgaa	actcaaatat	1860
tgacccagac	atgagcaatt	tgtttttcaa	atgctaaggg	atfttttaatz	gattttgcttt	1920
aattaaatct	agcctgtttc	taagctttat	tcattatftc	tccatactca	gagcattttct	1980
ccagatfttc	taaagaatag	aatftttattg	ctacatatca	tcagctatgc	ctgctgctat	2040
ttaatgggta	tctgaattaa	aaggctctgg	ttgtccctag	agaatcaaaz	tttttcttca	2100
ctcccatatt	tcagaacttg	atacatfttt	aggataaaac	atgaatgaca	cccgtttctt	2160
ctccctcacc	ctcccttccc	tcccattftt	tttttttttt	tttttttagaa	gctgaataaz	2220
atcaatgata	tccctgaagtc	cgtgttcttg	atcttcccac	atftttgcct	gggacgaggg	2280
ctcatcgaca	tggtgaaaaa	ccaggcaatz	gctgatgccc	tggaaaaggt	tggtgagtga	2340
agcagtggt	gtaggatgct	ttaatggaga	tggcactctg	cataggcctt	ggtaccctga	2400
actttgtttt	ggaaagaagc	aggtgactaa	gcacaggatz	ttccccacc	cccatgcccc	2460
gtgacagggc	tcattgccaac	acagctgggt	gtggcatggg	ttttgtgaca	caaccatttg	2520
tctgtgtctc	tgatagcatt	gagaaaaagt	aaagggcagt	tttgaaggta	aggaaaaatg	2580
tgttatttgc	ttggatccac	tggctcatgc	cactgtctgg	gttgggttaga	agcactggaa	2640
aagtcaaacc	ataactttga	gaattagggt	atcagggaat	cagaaggaaa	gatgcaaaat	2700
ttggctcttt	taggcgaatc	atgtgcctgc	agatgaggtc	atftattatc	ttttacacag	2760
tctataaaaz	tataatgtat	tacatctftt	tctaccttta	gaatggttaa	aaatattctc	2820
ccggtagcca	tatgattatt	attcatccat	tagataatat	agtcaaatzg	gccatgttat	2880
ttactgttca	tagaagaggg	gctttttgca	acttgggcta	caaaggagat	atgtaaggaa	2940
tttaagggaat	ggttacatgg	aactagattt	aattgaatct	agtgggttaa	ttgattcaat	3000
aggatatatz	ctactgaaag	gggaatctgc	ttaaagtgt	ttctgatatt	tattattact	3060
aaaacttaga	atftattaaa	aatactgact	gtgaaaatta	cttgggtcgt	ttgcctfttt	3120
aaaaggattt	ttggcatgtc	tcattaaaaa	aagaaataat	agatatcttc	agtgaagtta	3180
caaatcgaat	acacattggc	tctgaaatct	tgattgatac	tgggtcataa	aaagtftttcc	3240
caaatcagac	ttggaaaagt	atcactctct	tgttactctt	ttttccttgt	catgggtgat	3300
agccatttgt	gtttatttga	agatcggtga	atfttaagga	acataggccc	aaatttgagg	3360
aagggccatg	gtttttgatc	cctccattct	gaccggatct	ctgcattgtg	tctactaggg	3420
gagaatcgct	ttgtgtcacc	attatctttg	gacttgggtg	gacgaaacct	cttcgccatg	3480
gccgtggaag	gggtgggtgt	cttcttcatt	actgttctga	tccagtacag	attcttcac	3540
aggcccaggt	gagctftttc	ttagaacctg	tggagcacct	ggttgagggg	cacagaggag	3600
gcgcacaggg	aaacactcac	caatgggggt	tgcattgaac	tgaactcaaa	atatgtgata	3660
aaactgattt	tcctgatgtg	ggcatcccgc	agccccctcc	ctgcccattc	tggagactgt	3720
ggcaagtagg	ttttataata	ctacgttaga	gactgaatct	ttgtcctgaa	aaatagtttg	3780
aaaggttcat	ttttcttgtt	ttttccccca	agacctgtaa	atgcaaagct	atctcctctg	3840
aatgatgaag	atgaagatgt	gaggcgggaa	agacagagaa	ttcttgatgg	tggaggccag	3900
aatgacatct	tagaaatcaa	ggagttgacg	aaggtgagag	agtacagggt	acaatagctc	3960
atcttcagtt	tttttcagct	ttatgtgctg	taaccacgca	gtttgtgac	ttgcttaata	4020
aaagggcatg	tgttcccaaa	atgtacatct	ataccaaggt	tctgtcaatt	ttattttaaa	4080
aacaccatgg	agacttctta	aagaattctt	actgagaatt	cttttgtgat	atgaattccc	4140
attctcgaat	actttggttt	tatatgctta	catttatgtg	ttagtatta	aaacatacta	4200
atattgtata	tctagtcaaa	ctgagtagag	agataatgg	gatt		4244

<210> 28

<211> 5023

<212> DNA

<213> Homo sapiens

<400> 28

ttttaaaata	cctgcaatac	atatatatgt	tgaatagatz	aaaaattatz	tagatgataa	60
tgaatgatac	ggttctaaaa	agacagggtta	aaaagtaagt	tcactftttat	tttgagcttc	120
agaatcattc	agaagccagt	cgccacaaac	gcagaccaag	gctcttggca	catcaaatat	180
gcctatggct	taggggttatt	gacaagtctt	atgttgcagt	gtatgtgggt	tatagtcctg	240
ccttccacag	ttgcttggga	gagctgtgag	tcactgaggc	ttatgaatgt	ttacattttg	300

tttgttgacag	atatatagaa	ggaagcggaa	gcctgctggt	gacaggattt	gcgtgggcat	360
tcctcctgggt	gaggtaaaga	cactttgtct	atattgcgtt	tgtccctatt	agttcagact	420
atctctaccc	aatcaagcaa	cgatgctcgt	taagaggtaa	aagtggattt	taaaggcttc	480
tgtatttatg	ccaggatgga	gcaattagtc	atcgagaaga	gagggaccct	gtatgtcaag	540
agaatgattt	cagagaatcc	aatacaattt	aagaaaaagc	atggggctgg	gcgcagtgat	600
tcactcctgt	aatcccagca	ctttgggagg	ccgagggtgg	cggactcacg	aggtcaggag	660
attgagacca	tcctggccaa	catggtgaaa	ccccatctct	actataaata	caaaaattag	720
ctgggcatag	tagtgcattc	ctgtagtccc	agctactcgg	gaggctgagg	caggagaatt	780
gcttgaacct	aggaggggga	ggttgcccag	attgcgctgc	tgcactccag	cctggtgaca	840
gagtggagact	catgtcaaca	acaaaaacag	aaaaagcacg	cacatctaaa	acatgctttt	900
gtgatccatt	tgggatgggtg	atgacattca	aatagttttt	taaaaataga	ttttctcctt	960
tctgggtttcc	gtttgtgttc	ttttatgccc	ttttgccaga	gtaggtgggtg	caatttggtc	1020
agctggctttt	cattactggt	tttcacacat	taactttggc	ctcaacttga	caactcaaat	1080
aatattttata	aatacagcca	cacttaaaat	ggtcccatta	tgaaatacat	atttaaatat	1140
ctatacgatg	tgttaaaacc	aagaaaatat	ttgattcttc	tctgatattt	aagaattgaa	1200
ggtttgagggt	agttacgtgt	taggggcatt	tatattcatg	tttttagagt	ttgcttatac	1260
aacttaatct	ttccttttca	gtgctttggg	ctcctgggag	ttaatggggc	tggaaaatca	1320
tcaacttttca	agatgttaac	aggagatacc	actgttacca	gaggagatgc	tttccttaac	1380
aaaaataggt	gagaaaagaa	gtggcttgta	ttttgctgca	aagactttgt	ttttaattta	1440
tttaaagaaa	taggttggtta	tttttgatta	cagtgggtatt	tttagagtcc	ataaaaaatgt	1500
tgaaatatag	taaagggttaa	agaagcacat	aaaatcatcc	atgatttcaa	tatctagaga	1560
taatcacaa	ttacatttcc	tttcagtctc	attctcttct	tttaacagct	ttattcagggt	1620
ataattttaca	tacaatataa	tttgcttggt	ttttaagagt	ataatttagt	gatttttggt	1680
aaattgagag	ttttgcaacc	atcaccacaa	tccagtttta	gaacttttcc	atcacccac	1740
atctgtctta	tatacacata	taaagtgtgc	atacaattga	gatcatactg	tatgtagaat	1800
ttaaaattag	tttttattgt	taatgagtgt	attatgaata	tttcccagtg	ggttacattt	1860
cctaagatgt	ggaattttac	attgctacat	aaaatcccc	tatgtacatg	tacctataat	1920
ttattttaata	aattccttat	aaatggttga	cacattagtt	tccatttttc	actatgtaaa	1980
tatgtccctg	tatacatctt	ttattatttc	ctcaggaaca	attcctacaa	agtaaatgac	2040
cctctctaaa	gagcatataa	attgactgag	ccaccgttag	gccattttct	gagactgcac	2100
aggtcacaaa	gcaatctgat	ctttgggaat	acagctacat	tttataggct	tcttagataa	2160
tgttactcta	agtactttaa	atatgtgggg	cttctctggg	cttttttttt	tttgagacgg	2220
agtttcaactc	ttactgccc	ggctggagag	caatggcgcg	accttggtctc	actgcaacct	2280
ccgcctccca	ggttcaagcg	attctcctgc	ctcagcctcc	tgagtagctg	agattacagg	2340
tgcccgcac	aatgcctgcc	taattttttt	gtatttttcag	tagagatggg	gtttcaccat	2400
gttggccaga	ctggtctcga	gctcctgacc	tcagggtgatc	cacctgcctc	agcctcccaa	2460
agttctggga	ttacaggcat	gagccactgc	gcccggcttc	tctggactta	ttatgtggag	2520
agatagtaca	aggcagtggc	tttcagagtt	ttttgaccat	gaccgttgtg	ggaaatacat	2580
tttatatctc	aacctagtat	gtacacacag	acatgtagac	acatgtataa	cctaaagttt	2640
cataaagcag	tacctactgt	tactaattgt	agtgcactct	gctatttctt	attctacctt	2700
atactgcgtc	attaaaaaag	tgtgtgtcat	gaccactaa	atttatttcc	caaaccacta	2760
atgaacaatg	actcacaatt	tgaacacact	ggacaggggg	atagccaata	aaattgaaaa	2820
gagcaaggaa	attaatgtat	tcatgatctc	ctctcctgtc	tcttacattt	ttgcagtagc	2880
aatgtaaagg	aatcctaaga	gaacagacat	tctgggaata	gcaggcctag	cgctgcacaa	2940
ctgctttcct	aggcttgctc	ctagtaccaa	gctcctgacg	catatagcag	tggcagtaat	3000
aaccagccca	tagtaagggt	tgtcacaggg	actgggtgta	agaactgatt	tgrttggtat	3060
agctgtgagg	gcctggcacg	gtgtocacgt	gtgcctcaat	cctaattctg	aaaaaggctg	3120
accctggggg	tgctaattag	atacacagag	aggaatgaat	gctgccagaa	ggccaagtcc	3180
atggcaatgc	cgctgtggct	gaggtgcagt	catcagtctg	gaacgtgaac	actgaacttc	3240
tctcacatgt	gattcttcac	ttgactggct	tcatagaacc	ccaaagccac	cccaccacca	3300
cataaattgt	gtctctaggt	tctgtgttgc	tcacactcaa	aatttctggg	ccttctcatt	3360
tgggtgcatgt	gaatgggtgca	tatgagtga	gctcaggatg	gggccttagc	gttaaagccc	3420
tggggtagtg	tgactgagat	tgttggttaa	gaatgtgcag	tgggtggcat	gacctcagaa	3480
attctgaaat	gggactgcac	ctgcagactg	aagtgttcag	agagccaggg	aggtgcaagg	3540
actggggagg	gtagaggcag	gaaccctgcc	tgccaggaag	agctagcatc	ctgggggcag	3600

aaaggctgtg	ctttcaagta	gcagcagatg	tattgggtatc	tttgtaatgg	agaagcatatc	3660
tttacaggaa	cattaggcca	gattgtctaa	ccagagtatc	tctacctgct	taaaatctaa	3720
gtagttttct	tgtcctttgc	agtatcttat	caaacatcca	tgaagtacat	cagaacatgg	3780
gctactgccc	tcagtttgat	gccatcacag	agctgttgac	tgggagagaa	cacgtggagt	3840
tctttgccct	tttgagagga	gtcccagaga	aagaagttgg	caaggtagctg	tgggcacctg	3900
aaagccagcc	tgtctccttt	ggcatcctga	caatatatac	cttatggctt	ttccacacgc	3960
attgacttca	ggctgttttt	cctcatgaat	gcagcagcac	aaaatgctgg	ttctttgtat	4020
ctgctttcag	ggtaggaacc	tgtaacggtg	gtggggcagg	gctgggtggg	cagagagggg	4080
gtgctgctcc	caccacacga	gtcccttctc	cctgctttgg	ctcctcacca	gttgtcaggt	4140
tatgattata	gaatctagtc	ctactcagtg	aaagaacttt	catacatgta	tgtgtaggac	4200
agcatgataa	aattcccaag	ccagaccaaa	gtcaagggtgc	tttttatcac	tgtagggttg	4260
tgagtgggcg	attcggaaac	tgggcctcgt	gaagtatgga	gaaaaatatg	ctggtaacta	4320
tagtggaggc	aacaaacgca	agctctctac	agccatggct	ttgatcggcg	ggcctcctgt	4380
ggtgtttctg	gtgagtataa	ctgtggatgg	aaaactgttg	ttctggcctg	agtggaaaaac	4440
atgactgttc	aaaagtccta	tatgtccagg	gctgttgat	gattggcttg	tcttccccca	4500
gggacagcag	agcaaccttg	gaaaagcaga	gggaagcttc	tcccttggca	cacactgggg	4560
tggctgtacc	atgcctgcag	atgctcccaa	atagaggcac	tccaagcact	ttgtttctta	4620
gcgtgattga	ggctggatat	gtgatttgat	ctttctctgg	aacattcttt	ctaattcatct	4680
ttgtgttcat	tccctgaaaa	tgaagagtgt	ggacacagct	ttaaaatccc	caaggtagca	4740
actaggtcat	agttccttac	acacggatag	atgaaaaaca	gatcagactg	ggaagtggcc	4800
cttgaccttt	tttcttctgt	agataagagc	attgatgtta	ttacgggaag	aagcctttga	4860
ggcttttatg	tattccacct	cggctctggaa	tttgtttctg	taaggctaac	agttgcaata	4920
tactagggtg	atctgagtga	gctggaatta	aaaaaaaaaa	ggaatttcac	cccaatctta	4980
tactgacttc	aatagaggtt	tcagacaaaa	agttgttttg	tat		5023

<210> 29

<211> 5138

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (5138)

<223> n = a, t, c, or g

<400> 29

ngccnngttn	aaaangaaaa	tttnnnnnaa	attnaanntt	anngngnnnn	tttccccaga	60
aaaaacnaaa	angatttccn	cccngggggg	ncccccnant	cnaaaaggcc	ccncttnttt	120
gnngngaggg	aaagnttttt	ttggaatttt	taattttttg	tcccccaaaa	cctattattg	180
agaattttaat	tacataaaaa	agtactcaga	atattttgagt	ttcctgcac	aataagacat	240
ttataataat	gaccttggtt	acaaatgaat	ttgaaagtta	ctctaattct	ttgattcatc	300
aagaaataac	tagaatggca	agttaaaatt	taagctgttt	caaagatgct	tctgcattta	360
aaaacaaatt	tatctttgat	tttttttccc	cccagcaaat	aagacttatt	ttattctaatt	420
tacaggatga	acccaccaca	ggcatggatc	ccaaagcccg	gcggttcttg	tgggaattgtg	480
ccctaagtgt	tgtcaaggag	gggagatcag	tagtgcttac	atctcatagg	tccgtagtaa	540
agtcctgggt	tcctcactgt	gggatgtttt	aactttccaa	gtagaatatg	cgatcatttt	600
gtaaaaaatta	gaaaaatacag	aaaagcaaa	agtaaaaaca	ttattacctg	aaattatata	660
tgcataattct	tacaaaaatg	caagcccagt	ataaaactgt	ctctttttca	cttaatatat	720
tgtaaacatt	attccaagtc	agtgcattta	gggtgcattt	cttatagctg	gatagtattc	780
cattaggata	tactcttatt	taactattcc	cccttttgta	gacatttgga	ttatttccaa	840
cttgttcaca	attgtaaaca	ccactacact	gaacagcatc	atccctatat	ccacatgtac	900
ttgtaacaga	atacaattcc	ctaggaagct	ggaatgctgg	aagtcatggg	gatgttctca	960
tggttacaga	gaatctctct	aaaactaaaa	cctctttctg	ttttaccgca	gtatggaaga	1020

atgtgaagct	ctttgcacta	ggatggcaat	catgggtcaat	ggaagggttca	ggtgccttgg	1080
cagtgtccag	catctaaaaa	ataggttaata	aagataat	ctttgggata	gtgccttagtg	1140
agaaggcttg	atatttat	ttttgtgagt	atataaat	tgctctctaaa	ataaagggaa	1200
ataaaactga	gcaaaacagt	atagtggaaa	gaatgagggc	tttgaagtcc	gaactgcatt	1260
caaattctgt	ctttaccatt	tactgggttct	gtgactcttg	ggcaagttac	ttaactactg	1320
taagagttag	tttccctgga	agatctacct	cctagccttg	tgctatagat	gaaatgaaaa	1380
aaatttacat	gtgccagtac	tgggtgagagc	gcaagctttg	gagtcaaaaca	caaaggggtt	1440
tgcacctcgtg	ccctaccaat	tatgagctct	gagccatggg	caagtgacta	actccctggg	1500
cctcagtttc	tctgtaacat	ctgtcagact	tcatgggtcc	aggtgaggat	taaaggagat	1560
catgtattta	cagcacatgg	catgggtgctt	cacataaaat	aagtatttag	taaatgataa	1620
ctgggtccctt	ctctcagaaa	cttatttctg	ggcctgccag	gggccgccct	ttttcatggc	1680
acaagttggg	ttcccagggg	tcagtattct	tttaaatagt	tttctggaga	tcctccattt	1740
gggtattttt	tctgtctttc	aggtttggag	atgggttatac	aatagttgta	cgaatagcag	1800
gggtccaaacc	ggacctgaag	cctgtccagg	atttcttttg	acttgcattt	cctggaagt	1860
ttcyaaaaga	gaaacaccgg	aacatgctac	aataccagct	tccatcttca	ttatcttctc	1920
tggccaggat	attcagcatc	ctctcccaga	gcaaaaagcg	actccacata	gaagactact	1980
ctgtttctca	gacaacactt	gaccaagtaa	gctttgagtg	tcaaaacaga	tttacttctc	2040
aggggtgtgga	ttcctgcccc	gacactcccg	cccatagggtc	caagagcagt	ttgtatcttg	2100
aattgggtgct	tgaattcctg	atctactatt	cctagctatg	ctttttacta	aacctctctg	2160
aacctgaaaa	gggagatgat	gcctatgtac	tctataggat	tattgtgaga	atttactgta	2220
ataataacca	taaaaactac	catttagtga	gcacctacca	tgggccaggc	attttacttg	2280
gtgcctaatac	ctattttaaat	tagataaaaa	agtaccaa	aggtcctgac	acttaagaag	2340
tactcagtaa	atattttctt	ccctcttccc	tttaatcaag	accgtatgtg	ccaaagtaaa	2400
tggatgactg	agcagttggg	gatgtagggg	tggggggcgga	tatagaaagt	cagtttttgg	2460
ccgggcgtgg	tggtcatgc	ctgtaatccc	agcactttgg	gaggctgagg	agcaggcaga	2520
tcattgaggtc	aggagatcca	gataatcctg	gccaacaggg	tgaaaccccg	tctctactaa	2580
aaatacaaaa	attagctggg	catgggtggg	cgcacttgta	gtcccagcta	cttgcgaggc	2640
tgaggcagga	gaattgctcg	aaccaggag	gtggagggtta	cagtgagcca	aggtctcgcc	2700
actgcactcc	agcctgggga	cagagcaaga	ccccatttca	aggggggaaa	aaaagtctat	2760
ttttaagttg	ttattgcttt	tttcaagtat	tcttccctcc	ttcacacaca	gttttctagt	2820
taatccattt	atgtaattct	gtatgctcct	acttgacctt	atttcaacat	ctggaaaaat	2880
agaactagaa	taaagaatga	gcaagttgag	tgggtatttat	aaaggtccat	cttaattctt	2940
taacagggtat	ttgtgaactt	tgccaaggac	caaagtgatg	atgaccactt	aaaagacctc	3000
tcattacaca	aaaaccagac	agtagtggac	gttgcagttc	tcacatcttt	tctacaggat	3060
gagaaagtga	aagaaagcta	tgtatgaaga	atcctgttca	tacgggggtg	ctgaaagtaa	3120
agaggaaacta	gactttcctt	tgcaccatgt	gaagtgttgt	ggagaaaaga	gccagaagtt	3180
gatgtgggaa	gaagtaaaact	ggatactgta	ctgatactat	tcaatgcaat	gcaattcaat	3240
gcaatgaaaa	caaaattcca	ttacaggggc	agtgcccttg	tagcctatgt	cttgtatggc	3300
tctcaagtga	aagacttgaa	tttagttttt	tacctatacc	tatgtgaaac	tctattatgg	3360
aacccaatgg	acatatgggt	ttgaactcac	actttttttt	ttttttttgt	tcctgtgtat	3420
tctcattggg	gttgcaacaa	taattcatca	agtaatcatg	gccagcgatt	attgatcaaa	3480
atcaaaaagg	aatgcacatc	ctcattcact	aagccatgcc	atgccagga	gactggtttc	3540
ccggtgacac	atccattgct	ggcaatgagt	gtgccagagt	tattagtgcc	aagtttttca	3600
gaaagtttga	agcaccatgg	tgtgtcatgc	tcacttttgt	gaaagctgct	ctgctcagag	3660
tctatcaaca	ttgaatatca	gttgacagaa	tgggtgccatg	cgtggctaac	atcctgcttt	3720
gattccctct	gataagctgt	tctgggtggca	gtaacatgca	acaaaaatgt	gggtgtctcc	3780
aggcacggga	aacttggttc	cattgtttata	ttgtcctatg	cttcgagcca	tgggtctaca	3840
gggtcatcct	tatgagactc	ttaaatatac	ttagatcctg	gtaagaggca	agaatcaac	3900
agccaaaactg	ctggggctgc	aactgctgaa	gccagggcat	gggattaaag	agattgtgcg	3960
ttcaaaccta	gggaagcctg	tgccatttgg	tcctgactgt	ctgctaacat	ggtacactgc	4020
atctcaagat	gtttatctga	cacaagtgtta	ttatttctgg	ctttttgaat	taatctagaa	4080
aatgaaaaga	tggagtgtga	ttttgacaaa	aatgtttgtta	ctttttaatg	ttatttgga	4140
ttttaagttc	tatcagtgc	ttctgaatcc	ttagaatggc	ctcctttag	aacctgtgg	4200
tatagaggag	tatggccact	gcccactatt	tttattttct	tatgtaagtt	tgcataatcag	4260
tcattgactag	tgccatgaaa	gcaatgtgat	ggtcaggatc	tcattgacatt	atattttgagt	4320

ttcttttcaga	tcattttagga	tactcttaat	ctcacttcat	caatcaaata	ttttttgagt	4380
gtatgctgta	gctgaaagag	tatgtacgta	cgtataagac	tagagagata	tttaagtctca	4440
gtacacttcc	tgtgccatgt	tattcagctc	actggtttac	aaatataggt	tgtcttgtgg	4500
ttgtaggagc	ccactgtaac	aatactgggc	agcctttttt	tttttttttt	taattgcaac	4560
aatgcaaaaag	ccaagaaaag	ttaaggggtca	caagtctaaa	caatgaattc	ttcaacaggg	4620
aaaacagcta	gcttgaaaac	ttgctgaaaa	acacaacttg	tgtttatggc	atttagtacc	4680
ttcaaataat	tggcctttgca	gatattggat	acccatttaa	atctgacagt	ctcaaatttt	4740
tcatctcttc	aatcactagt	caagaaaaaa	tataaaaaaca	acaaatactt	ccatatggag	4800
cattttttcag	agtttttctaa	cccagtctta	tttttctagt	cagtaaacad	ttgtaaaaat	4860
actgtttcac	taatacttac	tgtaactgt	cttgagagaa	aagaaaaata	tgagagaact	4920
attgtttggg	gaagttcaag	tgatctttca	atatcattac	taacttcttc	cactttttcc	4980
agaatttgaa	tattaacgct	aaagggtgaa	gacttcagat	ttcaaattaa	tctttctata	5040
ttttttaaat	ttacagaata	ttatataacc	cactgctgaa	aaagaaacaa	atgattgttt	5100
tagaagttaa	aggtcaatat	tgatttttaa	atattaag			5138

<210> 30

<211> 20

<212> DNA

<213> Homo sapiens

<400> 30

gtgttcctgc agagggcatg

20

<210> 31

<211> 20

<212> DNA

<213> Homo sapiens

<400> 31

cacttccagt aacagctgac

20

<210> 32

<211> 21

<212> DNA

<213> Homo sapiens

<400> 32

ctttgcgcat gtccttcatg c

21

<210> 33

<211> 21

<212> DNA

<213> Homo sapiens

<400> 33

gacatcagcc ctcagcatct t

21

<210> 34

<211> 19

<212> DNA

<213> Homo sapiens

<400> 34

41

caacaagcca tgttccctc

19

<210> 35

<211> 18

<212> DNA

<213> Homo sapiens

<400> 35

catgttccct cagccagc

18

<210> 36

<211> 19

<212> DNA

<213> Homo sapiens

<400> 36

cagagctcac agcagggac

19

<210> 37

<211> 21

<212> PRT

<213> Homo sapiens

<400> 37

Cys Ser Val Arg Leu Ser Tyr Pro Pro Tyr Glu Gln His Glu Cys His

1

5

10

15

Phe Pro Asn Lys Ala

20

<210> 38

<211> 14

<212> DNA

<213> Homo sapiens

<400> 38

gcctgtgtgt cccc

14

<210> 39

<211> 14

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (14)

<223> n = t or c

<400> 39

gcctgtgngt cccc

14

<210> 40

<211> 45

<212> DNA

<213> Homo sapiens

42

<400> 40

aagaagatgc tgcctgtgtg tccccccaggg gcagggggggc tgcct

45

<210> 41

<211> 15

<212> PRT

<213> Homo sapiens

<400> 41

Lys	Lys	Met	Leu	Pro	Val	Cys	Pro	Pro	Gly	Ala	Gly	Gly	Leu	Pro
1				5					10				15	

<210> 42

<211> 15

<212> PRT

<213> Mus musculus

<400> 42

Lys	Lys	Met	Leu	Pro	Val	Cys	Pro	Pro	Gly	Ala	Gly	Gly	Leu	Pro
1				5					10				15	

<210> 43

<211> 15

<212> PRT

<213> Homo sapiens

<400> 43

Lys	Lys	Met	Leu	Pro	Val	Arg	Pro	Pro	Gly	Ala	Gly	Gly	Leu	Pro
1				5					10				15	

<210> 44

<211> 5

<212> PRT

<213> Caenorhabditis elegans

<400> 44

Leu	Leu	Gly	Gly	Ser
1				5

<210> 45

<211> 45

<212> DNA

<213> Homo sapiens

<400> 45

aagaagatgc tgcctgtgcg tccccccaggg gcagggggggc tgcct

45

<210> 46

<211> 14

<212> DNA

<213> Homo sapiens

<400> 46

gcctacttgc agga

14

43

<210> 47
 <211> 14
 <212> DNA
 <213> Homo sapiens

<400> 47
 gcctacttgc ggga

14

<210> 48
 <211> 45
 <212> DNA
 <213> Homo sapiens

<400> 48
 tgggggggct tcgcctactt gcaggatgtg gtggagcagg caatc

45

<210> 49
 <211> 15
 <212> PRT
 <213> Homo sapiens

<400> 49
 Trp Gly Gly Phe Ala Tyr Leu Gln Asp Val Val Glu Gln Ala Ile
 1 5 10 15

<210> 50
 <211> 15
 <212> PRT
 <213> Mus musculus

<400> 50
 Trp Gly Gly Phe Ala Tyr Leu Gln Asp Val Val Glu Gln Ala Ile
 1 5 10 15

<210> 51
 <211> 15
 <212> PRT
 <213> Homo sapiens

<400> 51
 Trp Gly Gly Phe Ala Tyr Leu Arg Asp Val Val Glu Gln Ala Ile
 1 5 10 15

<210> 52
 <211> 12
 <212> PRT
 <213> Caenorhabditis elegans

<400> 52
 Phe Met Thr Val Gln Arg Ala Val Asp Val Ala Ile
 1 5 10

<210> 53
 <211> 45
 <212> DNA

<213> Homo sapiens

<400> 53

tgggggggct tgcctactt gcgggatgtg gtggagcagg caatc

45

<210> 54

<211> 25

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(25)

<223> n is a, t, c, or g.

<400> 54

tcattcctct tgtngcnch gnnch

25

<210> 55

<211> 45

<212> DNA

<213> Homo sapiens

<400> 55

agtagcctca ttctcttct tgtgagcgct ggctgctag tggtc

45

<210> 56

<211> 15

<212> PRT

<213> Homo sapiens

<400> 56

Ser	Ser	Leu	Ile	Pro	Leu	Leu	Val	Ser	Ala	Gly	Leu	Leu	Val	Val
1				5				10					15	

<210> 57

<211> 15

<212> PRT

<213> Mus musculus

<400> 57

Ser	Ser	Leu	Ile	Pro	Leu	Leu	Val	Ser	Ala	Gly	Leu	Leu	Val	Val
1				5				10					15	

<210> 58

<211> 14

<212> PRT

<213> Homo sapiens

<400> 58

Ser	Ser	Leu	Ile	Pro	Leu	Val	Ser	Ala	Gly	Leu	Leu	Val	Val
1				5				10					

<210> 59

<211> 15

45

<212> PRT

<213> Caenorhabditis elegans

<400> 59

Ile Asn Tyr Ala Lys Leu Thr Phe Ala Val Ile Val Leu Thr Ile
1 5 10 15

<210> 60

<211> 42

<212> DNA

<213> Homo sapiens

<400> 60

agtagcctca ttcctcttgt gagcgctggc ctgctagtgg tc

42

<210> 61

<211> 25

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(25)

<223> n is a, t, c, or g.

<400> 61

tgatgaagat gananncngn ngcga

25

<210> 62

<211> 36

<212> DNA

<213> Homo sapiens

<400> 62

aatgatgaag atgaagatgt gaggcgggaa agacag

36

<210> 63

<211> 12

<212> PRT

<213> Homo sapiens

<400> 63

Asn Asp Glu Asp Glu Asp Val Arg Arg Glu Arg Gln
1 5 10

<210> 64

<211> 12

<212> PRT

<213> Mus musculus

<400> 64

Asn Asp Glu Asp Glu Asp Val Arg Arg Glu Arg Gln
1 5 10

<210> 65

46

<211> 10
<212> PRT
<213> Homo sapiens

<400> 65
Asn Asp Glu Asp Val Arg Arg Glu Arg Gln
1 5 10

<210> 66
<211> 15
<212> PRT
<213> Caenorhabditis elegans

<400> 66
Asp Glu Arg Asp Val Glu Asp Ser Asp Val Ile Ala Glu Lys Ser
1 5 10 15

<210> 67
<211> 30
<212> DNA
<213> Homo sapiens

<400> 67
aatgatgaag atgtgaggcg ggaaagacag 30

<210> 68
<211> 14
<212> DNA
<213> Homo sapiens

<400> 68
agttgtacga atag 14

<210> 69
<211> 14
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(14)
<223> n i s t o r c.

<400> 69
agttgtanga atag 14

<210> 70
<211> 20
<212> DNA
<213> Homo sapiens

<400> 70
ggctggatta gcagtcctca 20

<210> 71

<211> 20
<212> DNA
<213> Homo sapiens

<400> 71
ggatttccca gatcccagtg 20

<210> 72
<211> 20
<212> DNA
<213> Homo sapiens

<400> 72
gacagacttg gcatgaagca 20

<210> 73
<211> 20
<212> DNA
<213> Homo sapiens

<400> 73
gcacttggca gtcacttctg 20

<210> 74
<211> 20
<212> DNA
<213> Homo sapiens

<400> 74
cgtttctcca ctgtcccatt 20

<210> 75
<211> 20
<212> DNA
<213> Homo sapiens

<400> 75
acttcaagga cccagcttcc 20

<210> 76
<211> 24
<212> DNA
<213> Homo sapiens

<400> 76
tcggtttctt gtttgttaaa ctca 24

<210> 77
<211> 20
<212> DNA
<213> Homo sapiens

<400> 77
tcccaaggct ttgagatgac 20

<210> 78
<211> 19
<212> DNA
<213> Homo sapiens

<400> 78
ggctccaaag cccttgtaa 19

<210> 79
<211> 20
<212> DNA
<213> Homo sapiens

<400> 79
gctgctgtga tggggtatct 20

<210> 80
<211> 25
<212> DNA
<213> Homo sapiens

<400> 80
tttgtaaatt ttgtagtgct cctca 25

<210> 81
<211> 20
<212> DNA
<213> Homo sapiens

<400> 81
tagtcagccc ttgcctccta 20

<210> 82
<211> 20
<212> DNA
<213> Homo sapiens

<400> 82
aaaggggctt ggtaagggtg 20

<210> 83
<211> 20
<212> DNA
<213> Homo sapiens

<400> 83
gatgtggtgc tccctctagc 20

<210> 84
<211> 20
<212> DNA
<213> Homo sapiens

<400> 84
caagtgagtg cttgggattg 20

<210> 85
<211> 21
<212> DNA
<213> Homo sapiens

<400> 85
gcaaattcaa atttctccag g 21

<210> 86
<211> 20
<212> DNA
<213> Homo sapiens

<400> 86
tcaaggagga aatggacctg 20

<210> 87
<211> 20
<212> DNA
<213> Homo sapiens

<400> 87
ctgaaagttc aagcgagtg 20

<210> 88
<211> 20
<212> DNA
<213> Homo sapiens

<400> 88
tgcagactga atggagcatc 20

<210> 89
<211> 20
<212> DNA
<213> Homo sapiens

<400> 89
gccaggggac actgtattct 20

<210> 90
<211> 20
<212> DNA
<213> Homo sapiens

<400> 90
aggtcctctg ccttcactca 20

<210> 91
<211> 20
<212> DNA
<213> Homo sapiens

<400> 91
ccagtgctta ccctgctaa 20

<210> 92
<211> 21
<212> DNA
<213> Homo sapiens

<400> 92
cacacaacag agcttcttgg a 21

<210> 93
<211> 20
<212> DNA
<213> Homo sapiens

<400> 93
acctggaaca ggtgtggtgt 20

<210> 94
<211> 21
<212> DNA
<213> Homo sapiens

<400> 94
gggctaacat gccactcagt a 21

<210> 95
<211> 20
<212> DNA
<213> Homo sapiens

<400> 95
gtttgttgca gatggggaag 20

<210> 96
<211> 20
<212> DNA
<213> Homo sapiens

<400> 96
caccagaaga aggagcatgg 20

<210> 97
<211> 20
<212> DNA
<213> Homo sapiens

<400> 97
ctggactcgt agggatttgc 20

<210> 98
<211> 21
<212> DNA
<213> Homo sapiens

<400> 98
gcctgtcaca gagaaatgct t 21

<210> 99
<211> 21
<212> DNA
<213> Homo sapiens

<400> 99
ttacggaatg atcctgtgct c 21

<210> 100
<211> 20
<212> DNA
<213> Homo sapiens

<400> 100
agtcagggttt ccggtcacac 20

<210> 101
<211> 22
<212> DNA
<213> Homo sapiens

<400> 101
ccgttcctta taccctcagg tg 22

<210> 102
<211> 21
<212> DNA
<213> Homo sapiens

<400> 102
ccttgtagac actcgactg a 21

<210> 103
<211> 20
<212> DNA
<213> Homo sapiens

<400> 103
tggtgtccac aggttccaga 20

<210> 104
<211> 20
<212> DNA
<213> Homo sapiens

<400> 104
tgagggttat gggcatggtt 20

<210> 105
<211> 20
<212> DNA
<213> Homo sapiens

<400> 105
atgtttttcc ttggctgtgc 20

<210> 106
<211> 20
<212> DNA
<213> Homo sapiens

<400> 106
atctgccctt tcttgtctga 20

<210> 107
<211> 20
<212> DNA
<213> Homo sapiens

<400> 107
agggagctgc acagtggata 20

<210> 108
<211> 24
<212> DNA
<213> Homo sapiens

<400> 108
tcactcccat atttcagaac ttga 24

<210> 109
<211> 22
<212> DNA
<213> Homo sapiens

<400> 109
tgttttattgg aagatcggtg aa 22

<210> 110
<211> 25
<212> DNA
<213> Homo sapiens

<400> 110
cgtttagagac tgaatctttg tcctg 25

<210> 111
<211> 20
<212> DNA
<213> Homo sapiens

<400> 111
agtcctgcct tccacagttg 20

<210> 112
<211> 21
<212> DNA
<213> Homo sapiens

<400> 112
ggtagttacg tgtaggggc a 21

<210> 113
<211> 21
<212> DNA
<213> Homo sapiens

<400> 113
caggaacatt aggccagatt g 21

<210> 114
<211> 23
<212> DNA
<213> Homo sapiens

<400> 114
catgtatgtg taggacagca tga 23

<210> 115
<211> 21
<212> DNA
<213> Homo sapiens

<400> 115
ctgtttcaaa gatgcttctg c 21

<210> 116
<211> 20
<212> DNA
<213> Homo sapiens

<400> 116
cctaggaagc tggaatgctg 20

<210> 117
<211> 20
<212> DNA
<213> Homo sapiens

<400> 117
gggttcccag ggttcagtat 20

<210> 118
<211> 23
<212> DNA
<213> Homo sapiens

<400> 118
cttgacctaa tttcaacatc tgg 23

<210> 119
<211> 20
<212> DNA
<213> Homo sapiens

<400> 119
atccccaact caaaaccaca 20

<210> 120
<211> 21
<212> DNA
<213> Homo sapiens

<400> 120
aagtccaatt tagcccacgt t 21

<210> 121
<211> 20
<212> DNA
<213> Homo sapiens

<400> 121
ccagccattc aaaattctcc 20

<210> 122
<211> 20
<212> DNA
<213> Homo sapiens

<400> 122
ggtgcaggtc aatttccaat 20

<210> 123
<211> 20
<212> DNA
<213> Homo sapiens

<400> 123
ccccttcacc accattacaa 20

<210> 124
<211> 20
<212> DNA
<213> Homo sapiens

<400> 124
tgtccaagga aaagcctcac 20

<210> 125
<211> 20
<212> DNA
<213> Homo sapiens

<400> 125
aggacctctt gccagactca 20

<210> 126
<211> 20
<212> DNA
<213> Homo sapiens

<400> 126
aggagatgac acaggccaag 20

<210> 127
<211> 20
<212> DNA
<213> Homo sapiens

<400> 127
cgcacacctc tgaagctacc 20

<210> 128
<211> 20
<212> DNA
<213> Homo sapiens

<400> 128
acctcactca cacctgggaa 20

<210> 129
<211> 20
<212> DNA
<213> Homo sapiens

<400> 129
gcctcctgcc tgaaccttat 20

<210> 130
<211> 23
<212> DNA
<213> Homo sapiens

<400> 130
caaaatcatg acaccaagtt gag 23

<210> 131
<211> 20
<212> DNA
<213> Homo sapiens

<400> 131
catgcacatg cacacacata 20

<210> 132
<211> 20
<212> DNA
<213> Homo sapiens

<400> 132
ccttagcccg tggtgagcta 20

<210> 133
<211> 21
<212> DNA
<213> Homo sapiens

<400> 133
tgcttttatt cagggactcc a 21

<210> 134
<211> 20
<212> DNA
<213> Homo sapiens

<400> 134
cccatgcact gcagagattc 20

<210> 135
<211> 19
<212> DNA
<213> Homo sapiens

<400> 135
aaggcaggag acatcgctt 19

<210> 136
<211> 20
<212> DNA
<213> Homo sapiens

<400> 136
gggatcagca tggtttccta 20

<210> 137
<211> 20
<212> DNA
<213> Homo sapiens

<400> 137
gcttaagtcc cactcctccc 20

<210> 138
<211> 20
<212> DNA
<213> Homo sapiens

<400> 138
attttcctcc gcatgtgtgt 20

<210> 139
<211> 20
<212> DNA
<213> Homo sapiens

<400> 139
tcacagaagc ctagccatga 20

<210> 140
<211> 20
<212> DNA
<213> Homo sapiens

<400> 140
aacagagcag ggagatgggtg 20

<210> 141
<211> 20
<212> DNA
<213> Homo sapiens

<400> 141
tctgcacctc tctcctctg 20

<210> 142
<211> 20
<212> DNA
<213> Homo sapiens

<400> 142
actggggcca acattaatca 20

<210> 143
<211> 20
<212> DNA
<213> Homo sapiens

<400> 143
cttccccatc tgcaacaaac 20

<210> 144
<211> 20
<212> DNA
<213> Homo sapiens

<400> 144
gctaaaggcc atccaaagaa 20

<210> 145
<211> 20
<212> DNA
<213> Homo sapiens

<400> 145
tcaagtgcac ctgggcataa 20

<210> 146
<211> 20
<212> DNA
<213> Homo sapiens

<400> 146
tctgaagtcc attcccttgg 20

<210> 147
<211> 20
<212> DNA
<213> Homo sapiens

<400> 147
caatgtggca tgcagttgat 20

<210> 148
<211> 19
<212> DNA
<213> Homo sapiens

<400> 148
gaagctacca gcccatacct 19

<210> 149
<211> 20
<212> DNA
<213> Homo sapiens

<400> 149
catttcccc actgtttcag 20

<210> 150
<211> 20
<212> DNA
<213> Homo sapiens

<400> 150
ccaaggcttt cttcaatcca 20

<210> 151
<211> 20
<212> DNA
<213> Homo sapiens

<400> 151
gatccgttta acctgccaac 20

<210> 152
<211> 19
<212> DNA
<213> Homo sapiens

<400> 152
atgcccctgc caactttac 19

<210> 153
<211> 20
<212> DNA
<213> Homo sapiens

<400> 153
ctctgcagct gttcccctac 20

<210> 154
<211> 20
<212> DNA
<213> Homo sapiens

<400> 154
tatcaatcca tggccctgac 20

<210> 155
<211> 20
<212> DNA
<213> Homo sapiens

<400> 155
agagtccctg ccctccttct

20

<210> 156
<211> 20
<212> DNA
<213> Homo sapiens

<400> 156
aaggcagtca gcagtgtcaa

20

<210> 157
<211> 20
<212> DNA
<213> Homo sapiens

<400> 157
gggggaacatc ctgtgcttag

20

<210> 158
<211> 20
<212> DNA
<213> Homo sapiens

<400> 158
ccattggtga gtgtttccct

20

<210> 159
<211> 20
<212> DNA
<213> Homo sapiens

<400> 159
agtcagcaaa ctgctgggtt

20

<210> 160
<211> 20
<212> DNA
<213> Homo sapiens

<400> 160
attgctccat cctggcataa

20

<210> 161
<211> 23
<212> DNA
<213> Homo sapiens

<400> 161
tcatggatga ttttatgtgc ttc

23

<210> 162
<211> 20
<212> DNA
<213> Homo sapiens

<400> 162
gcgtgtggaa aagccataag 20

<210> 163
<211> 20
<212> DNA
<213> Homo sapiens

<400> 163
gccaatcata caacagccct 20

<210> 164
<211> 23
<212> DNA
<213> Homo sapiens

<400> 164
tgatcgcata ttctacttgg aaa 23

<210> 165
<211> 22
<212> DNA
<213> Homo sapiens

<400> 165
tccctttatt ttagaggcac ca 22

<210> 166
<211> 21
<212> DNA
<213> Homo sapiens

<400> 166
gatcaggaat tcaagcacca a 21

<210> 167
<211> 24
<212> DNA
<213> Homo sapiens

<400> 167
tgggttccat aatagagttt caca 24

<210> 168
<211> 22
<212> DNA
<213> Homo sapiens

<400> 168
tgtcagctgt tactggaagt gg 22

<210> 169
<211> 22
<212> DNA
<213> Homo sapiens

<400> 169
tgtcagctgc tgctggaagt gg 22

<210> 170
<211> 21
<212> DNA
<213> Homo sapiens

<400> 170
aggagctggc cgaagccaca a 21

<210> 171
<211> 21
<212> DNA
<213> Homo sapiens

<400> 171
aggagctggc tgaagccaca a 21

<210> 172
<211> 21
<212> DNA
<213> Homo sapiens

<400> 172
aatgatgccca ccaaacaaat g 21

<210> 173
<211> 21
<212> DNA
<213> Homo sapiens

<400> 173
aatgatgccca tcaaacaaat g 21

<210> 174
<211> 21
<212> DNA
<213> Homo sapiens

<400> 174
gaggtggctc cgatgaccac a 21

<210> 175
<211> 21
<212> DNA
<213> Homo sapiens

<400> 175
gaggtggctc tgatgaccac a 21

<210> 176
<211> 21
<212> DNA
<213> Homo sapiens

<400> 176
ttccttaaca gaaatagtat c 21

<210> 177
<211> 21
<212> DNA
<213> Homo sapiens

<400> 177
ttccttaaca aaaatagtat c 21

<210> 178
<211> 21
<212> DNA
<213> Homo sapiens

<400> 178
ggaagtgttc caaaagagaa a 21

<210> 179
<211> 21
<212> DNA
<213> Homo sapiens

<400> 179
ggaagtgttc taaaagagaa a 21

<210> 180
<211> 21
<212> DNA
<213> Homo sapiens

<400> 180
agtaaagagg gactagactt t 21

<210> 181
<211> 21
<212> DNA
<213> Homo sapiens

<400> 181
agtaaagagg aactagactt t 21

<210> 182
<211> 21
<212> DNA
<213> Homo sapiens

<400> 182
gcctacttgc aggatgtggt g 21

<210> 183
<211> 21
<212> DNA
<213> Homo sapiens

<400> 183
gcctacttgc gggatgtggt g 21

<210> 184
<211> 23
<212> DNA
<213> Homo sapiens

<400> 184
cctcattcct cttcttgtga gcg 23

<210> 185
<211> 20
<212> DNA
<213> Homo sapiens

<400> 185
cctcattcct cttgtgagcg 20

<210> 186
<211> 21
<212> DNA
<213> Homo sapiens

<400> 186
gcaggactac gtgggcttca c 21

<210> 187
<211> 21
<212> DNA
<213> Homo sapiens

<400> 187
gcaggactac atgggcttca c 21

<210> 188
<211> 21
<212> DNA
<213> Homo sapiens

<400> 188
aaaagtctac cgagatggga t 21

<210> 189
<211> 21
<212> DNA
<213> Homo sapiens

<400> 189
aaaagtctac tgagatggga t 21

<210> 190
<211> 21
<212> DNA
<213> Homo sapiens

<400> 190
ggccagatca cctccttcct g 21

<210> 191
<211> 21
<212> DNA
<213> Homo sapiens

<400> 191
ggccagatca tctccttcct g 21

<210> 192
<211> 21
<212> DNA
<213> Homo sapiens

<400> 192
acacaccaca tggatgaagc g 21

<210> 193
<211> 21
<212> DNA
<213> Homo sapiens

<400> 193
acacaccaca cggatgaagc g 21

<210> 194
<211> 21
<212> DNA
<213> Homo sapiens

<400> 194
cctggaagaa gtaagttaag t 21

<210> 195
<211> 21
<212> DNA
<213> Homo sapiens

<400> 195
cctggaagaa ctaagttaag t 21

<210> 196
<211> 21
<212> DNA
<213> Homo sapiens

<400> 196
gctgcctgtg tgtccccag g 21

<210> 197
<211> 21
<212> DNA
<213> Homo sapiens

<400> 197
gctgcctgtg cgtccccag g 21

<210> 198
<211> 22
<212> DNA
<213> Homo sapiens

<400> 198
tagccattat ggaattactg ct 22

<210> 199
<211> 21
<212> DNA
<213> Homo sapiens

<400> 199
tagccattat caattactgc t 21

<210> 200
<211> 26
<212> DNA
<213> Homo sapiens

<400> 200
gatgaagatg aagatgtgag gcggga 26

<210> 201
<211> 20
<212> DNA
<213> Homo sapiens

<400> 201
gatgaagatg tgaggcgga 20

<210> 202
<211> 21
<212> DNA
<213> Homo sapiens

<400> 202
aatagttgta cgaatagcag g 21

<210> 203
<211> 21
<212> DNA
<213> Homo sapiens

<400> 203
aatagttgta tgaatagcag g 21

<210> 204
<211> 21
<212> DNA
<213> Homo sapiens

<400> 204
acacgctggg ggtgctggct g 21

<210> 205
<211> 21
<212> DNA
<213> Homo sapiens

<400> 205
acacgctggg cgtgctggct g 21

<210> 206
<211> 20
<212> DNA
<213> Homo sapiens

<400> 206
gaccagccac ggcgtccctg 20

<210> 207
<211> 21
<212> DNA
<213> Homo sapiens

<400> 207
gaccagccac gggcgtccct g 21

<210> 208
<211> 22
<212> DNA
<213> Homo sapiens

<400> 208
cattttctta gaaaagagag gt 22

<210> 209
<211> 22
<212> DNA
<213> Homo sapiens

<400> 209
cattttctta gagaagagag gt 22

<210> 210
<211> 21
<212> DNA
<213> Homo sapiens

<400> 210
gaaaattagt atgtaaggaa g 21

<210> 211
<211> 21
<212> DNA
<213> Homo sapiens

<400> 211
gaaaattagt ctgtaaggaa g 21

<210> 212
<211> 25
<212> DNA
<213> Homo sapiens

<400> 212
cctccgcctg ccagggttcag cgatt 25

<210> 213
<211> 25
<212> DNA
<213> Homo sapiens

<400> 213
cctccgcctg ccgggttcag cgatt 25

<210> 214
<211> 25
<212> DNA
<213> Homo sapiens

<400> 214
tatgtgctga ccatgggagc ttggt 25

<210> 215
<211> 25
<212> DNA
<213> Homo sapiens

<400> 215
tatgtgctga ccgtgggagc ttggt 25

<210> 216
<211> 21
<212> DNA
<213> Homo sapiens

<400> 216
gtgacacca acggagtagg g 21

<210> 217
<211> 21
<212> DNA
<213> Homo sapiens

<400> 217
gtgacacca gcggagtagg g 21

<210> 218
<211> 21
<212> DNA
<213> Homo sapiens

<400> 218
agtatccctt gttcacgaga a 21

<210> 219
<211> 25
<212> DNA
<213> Homo sapiens

<400> 219
agtatccctc ccttggtcac gagaa 25

<210> 220
<211> 21
<212> DNA
<213> Homo sapiens

<400> 220
ctgggttcct gtatcacaac c 21

<210> 221
<211> 21
<212> DNA
<213> Homo sapiens

<400> 221
ctgggttcct atatcacaac c 21

<210> 222
<211> 21
<212> DNA
<213> Homo sapiens

<400> 222
ggcctaccaa gggagaaact g 21

<210> 223
<211> 21
<212> DNA
<213> Homo sapiens

<400> 223
ggcctaccaa aggagaaact g 21

<210> 224
<211> 20
<212> DNA
<213> Homo sapiens

<400> 224
tttaaagggg gtgattagga 20

<210> 225
<211> 20
<212> DNA
<213> Homo sapiens

<400> 225
tttaaagggg ttgattagga 20

<210> 226
<211> 22
<212> DNA
<213> Homo sapiens

<400> 226
gaagaaattt gtttttttga tt 22

<210> 227
<211> 22
<212> DNA
<213> Homo sapiens

<400> 227
gaagaaattt ttttttttga tt 22

<210> 228
<211> 21
<212> DNA
<213> Homo sapiens

<400> 228
gcgggcatcc cgaggagg g 21

<210> 229
<211> 21
<212> DNA
<213> Homo sapiens

<400> 229
gcgggcatcc tgaggagg g 21

<210> 230
<211> 21
<212> DNA
<213> Homo sapiens

<400> 230
agggaggggg gctgaagatc a 21

<210> 231
<211> 21
<212> DNA
<213> Homo sapiens

<400> 231
agggaggggg actgaagatc a 21

<210> 232
<211> 20
<212> DNA
<213> Homo sapiens

<400> 232
aggagccaaa cgctcattgt 20

<210> 233
<211> 21
<212> DNA
<213> Homo sapiens

<400> 233
aggagccaaa gcgctcattg t 21

<210> 234
<211> 21
<212> DNA
<213> Homo sapiens

<400> 234
aagccactgt ttttaaccag t 21

<210> 235
<211> 21
<212> DNA
<213> Homo sapiens

<400> 235
aagccactgt atttaaccag t 21

<210> 236
<211> 21
<212> DNA
<213> Homo sapiens

<400> 236
cgtgggcttc acactcaaga t 21

<210> 237
<211> 21
<212> DNA
<213> Homo sapiens

<400> 237
cgtgggcttc ccactcaaga t 21

<210> 238
<211> 21
<212> DNA
<213> Homo sapiens

<400> 238
tcacactcaa gatcttcgct g 21

<210> 239
<211> 21
<212> DNA
<213> Homo sapiens

<400> 239
tcacactcaa catcttcgct g 21

<210> 240
<211> 21
<212> DNA
<213> Homo sapiens

<400> 240
gcagcctcac ccgctcttcc c 21

<210> 241
<211> 21
<212> DNA
<213> Homo sapiens

<400> 241
gcagcctcac tcgctcttcc c 21

<210> 242
<211> 21
<212> DNA
<213> Homo sapiens

<400> 242
agaagagaat atcagaaatc t 21

<210> 243
<211> 21
<212> DNA
<213> Homo sapiens

<400> 243
agaagagaat gtcagaaatc t 21

<210> 244
<211> 21
<212> DNA
<213> Homo sapiens

<400> 244
gcgcagtgcc ctgtgtcctt a 21

<210> 245
<211> 21
<212> DNA
<213> Homo sapiens

<400> 245
gcgcagtgcg ctgtgtcctt a 21

<210> 246
<211> 21
<212> DNA
<213> Homo sapiens

<400> 246
gatctaaggt tgcattctg g 21

<210> 247
<211> 21
<212> DNA
<213> Homo sapiens

<400> 247
gatctaaggt ggctattctg g 21

<210> 248
<211> 23
<212> DNA
<213> Homo sapiens

<400> 248
ctcttctgtt agcacagaag aga 23

<210> 249
<211> 23
<212> DNA
<213> Homo sapiens

<400> 249
ctcttctgtt atcacagaag aga 23

<210> 250
<211> 21
<212> DNA
<213> Homo sapiens

<400> 250
cattctaggg atcatagcca t 21

<210> 251
<211> 21
<212> DNA
<213> Homo sapiens

<400> 251
cattctaggg gtcataagcca t 21

<210> 252
<211> 22
<212> DNA
<213> Homo sapiens

<400> 252
aagtacagtg ggaggaacag cg 22

<210> 253
<211> 22
<212> DNA
<213> Homo sapiens

<400> 253
aagtacagtg tgaggaacag cg 22

<210> 254
<211> 22
<212> DNA
<213> Homo sapiens

<400> 254
attcctaataa aatagaaatg ca 22

<210> 255
<211> 22
<212> DNA
<213> Homo sapiens

<400> 255
attcctaataa agtagaaatg ca 22

<210> 256
<211> 21
<212> DNA
<213> Homo sapiens

<400> 256
ggcccctgcc ttattattac t 21

<210> 257
<211> 21
<212> DNA
<213> Homo sapiens

<400> 257
ggcccctgcc gtattattac t 21

<210> 258
<211> 22
<212> DNA
<213> Homo sapiens

<400> 258
tgagagaatt acttgaaccc gg 22

<210> 259
<211> 22
<212> DNA
<213> Homo sapiens

<400> 259
tgagagaatt gcttgaaccc gg 22

<210> 260
<211> 21
<212> DNA
<213> Homo sapiens

<400> 260
tttgctgaaa caatcactga c 21

<210> 261
<211> 21
<212> DNA
<213> Homo sapiens

<400> 261
tttgctgaaa taatcactga c 21

<210> 262
<211> 22
<212> DNA
<213> Homo sapiens

<400> 262
aacctcagtt ccctcatctg tg 22

<210> 263
<211> 22
<212> DNA
<213> Homo sapiens

<400> 263
aacctcagtt tcctcatctg tg 22

<210> 264
<211> 21
<212> DNA
<213> Homo sapiens

<400> 264
ctggacacca gaaataatgt c 21

<210> 265
<211> 21
<212> DNA
<213> Homo sapiens

<400> 265
ctggacacca aaaataatgt c 21

<210> 266
<211> 21
<212> DNA
<213> Homo sapiens

<400> 266
tcctatgtgt cctccaccaa t 21

<210> 267
<211> 21
<212> DNA
<213> Homo sapiens

<400> 267
tcctatgtgt gctccaccaa t 21

<210> 268
<211> 21
<212> DNA
<213> Homo sapiens

<400> 268
aagaagtggc ttgtattttg c 21

<210> 269
<211> 21
<212> DNA
<213> Homo sapiens

<400> 269
aagaagtggc ctgtattttg c 21

<210> 270
<211> 23
<212> DNA
<213> Homo sapiens

<400> 270
aactgatttg attggtatag ctg 23

<210> 271
<211> 23
<212> DNA
<213> Homo sapiens

<400> 271
aactgatttg gttggtatag ctg 23

<210> 272
<211> 21
<212> DNA
<213> Homo sapiens

<400> 272
caggggtccaa cccggacctg a 21

<210> 273
<211> 21
<212> DNA
<213> Homo sapiens

<400> 273
caggggtccaa tccggacctg a 21

<210> 274
 <211> 22
 <212> DNA
 <213> Homo sapiens

 <400> 274
 ttgggaggct aaggcaggag aa 22

 <210> 275
 <211> 22
 <212> DNA
 <213> Homo sapiens

 <400> 275
 ttgggaggct gaggcaggag aa 22

 <210> 276
 <211> 15
 <212> DNA
 <213> Gallus gallus

 <400> 276
 accaggggaa tctcc 15

 <210> 277
 <211> 15
 <212> DNA
 <213> Gallus gallus

 <400> 277
 accagggaaa tctcc 15

 <210> 278
 <211> 45
 <212> DNA
 <213> Gallus gallus

 <400> 278
 cgctacccaa caccagggga atctcctggt attgttgga acttc 45

 <210> 279
 <211> 15
 <212> PRT
 <213> Homo sapiens

 <400> 279
 Arg Tyr Pro Thr Pro Gly Glu Ala Pro Gly Val Val Gly Asn Phe
 1 5 10 15

 <210> 280
 <211> 15
 <212> PRT
 <213> Mus musculus

 <400> 280

77

Arg Tyr Pro Thr Pro Gly Glu Ala Pro Gly Val Val Gly Asn Phe
 1 5 10 15

<210> 281

<211> 15

<212> PRT

<213> Gallus gallus

<400> 281

Arg Tyr Pro Thr Pro Gly Glu Ser Pro Gly Ile Val Gly Asn Phe
 1 5 10 15

<210> 282

<211> 15

<212> PRT

<213> Gallus gallus

<400> 282

Arg Tyr Pro Thr Pro Gly Lys Ser Pro Gly Ile Val Gly Asn Phe
 1 5 10 15

<210> 283

<211> 45

<212> DNA

<213> Gallus gallus

<400> 283

cgctacccaa caccagggaa atctcctggt attgttgga acttc

45

<210> 284

<211> 19

<212> DNA

<213> Homo sapiens

<400> 284

gcgtcagggg tggggacag

19

<210> 285

<211> 20

<212> DNA

<213> Homo sapiens

<400> 285

gcgtcagggg ttggggacag

20

<210> 286

<211> 17

<212> DNA

<213> Homo sapiens

<400> 286

ccacttcggt ctccatg

17

<210> 287

<211> 17

<212> DNA
<213> Homo sapiens

<400> 287
ccacttcgat ctccatg

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.